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## RESEARCH & DEVELOPMENT DAY

June 26, 2025 – New York

# Safe Harbor Statement

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This presentation contains forward-looking statements. Crinetics Pharmaceuticals, Inc. (“Crinetics,” the “company,” “we,” “us,” or “our”) cautions you that all statements other than statements of historical facts contained in this presentation are forward-looking statements, including, but not limited to, statements regarding: the potential for any of our ongoing clinical trials to demonstrate safety or efficacy, plans and timing for CRN09682 trials targeting the treatment of patients with NETs, the potential expansion to further indications and complementary treatment with paltusotine; the potential clinical benefits of our TSHR antagonist, CRN12755, in patients across multiple indications, and the plans for advancement of such program, including future updates and potential studies; the potential benefits, safety and tolerability of our SST3 agonist, CRN10329, for autosomal dominant polycystic kidney disease, and the plans for advancement and growth of such program, including potential future public updates, studies, approval timeline, and expansion of treatment; development plans for our SST2 nonpeptide drug conjugates platform; development of possible new therapeutic options for neuroendocrine neoplasms; the anticipated timing of upcoming milestones of our development programs, clinical trials and registration applications of our product candidates; and the direction or trajectory of the Company’s potential future growth, and our expected plans and timing for commercialization of paltusotine and other product candidates pending regulatory approval. In some cases, you can identify forward-looking statements by terms such as “may,” “believe,” “anticipate,” “could,” “should,” “estimate,” “expect,” “intend,” “plan,” “project,” “will,” “predict,” “forecast,” “continue,” “lead to,” “designed to,” “goal,” “target,” and similar terms or the negatives thereof. These statements speak only as of the date of this presentation, involve known and unknown risks, uncertainties, assumptions, and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, without limitation: topline and initial data that we report may change following a more comprehensive review of the data related to the clinical studies and such data may not accurately reflect the complete results of a clinical study, and the FDA and other regulatory authorities may not agree with our interpretation of such results; the risk that interim or preclinical results of a clinical trial do not necessarily predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, and as more patient data become available; the possibility of unfavorable new clinical data and further analyses of existing clinical data; potential delays in the commencement, enrollment and completion of clinical trials and the reporting of data therefrom; our dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the success of our clinical trials and nonclinical studies for paltusotine and our other product candidates; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval and/or commercialization; our ability to obtain and maintain intellectual property protection for our product candidates; we may use our capital resources sooner than we expect; and other risks described under the heading “Risk Factors” in documents we file from time to time with the Securities and Exchange Commission. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and, except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

# Speakers



**SCOTT STRUTHERS, Ph.D.**

Founder and  
Chief Executive Officer



**STEPHEN BETZ, Ph.D.**

Founder and  
Chief Scientific Officer



**RICK GRIMES**

Global Product  
Leader, TSH



**STACEY HARTE**

Global Product  
Leader, NDC



**DAVID C. METZ, MBBCH**

Professor of Medicine (retired)  
Neuroendocrinologist

# AGENDA

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## INTRODUCTION

- Strategic Focus
- Discovery Overview

## SESSION 1

- **CRN12755: TSH**  
Grave's Hyperthyroidism, Graves' Orbitopathy (TED)
- **CRN10329: SST3**  
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

## BREAK

## SESSION 2

- **CRN09682: SST2 + NDC**
  - Non-Peptide Drug Conjugate (NDC) Platform and CRN09682
  - Neuroendocrine Tumors (NETs) and Carcinoid Syndrome

## CLOSING

## Q&A

# INTRODUCTORY REMARKS

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**Scott Struthers, Ph.D.**

Founder & Chief Executive Officer



# Serving our Patients

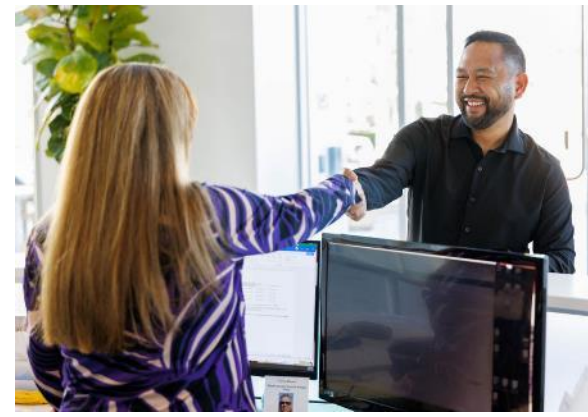
Our mission is to build the world's leading endocrine company that consistently pioneers new therapeutics to help patients better control their disease and improve their daily lives.



We made a **commitment** to the acromegaly community  
**And we stand by it**



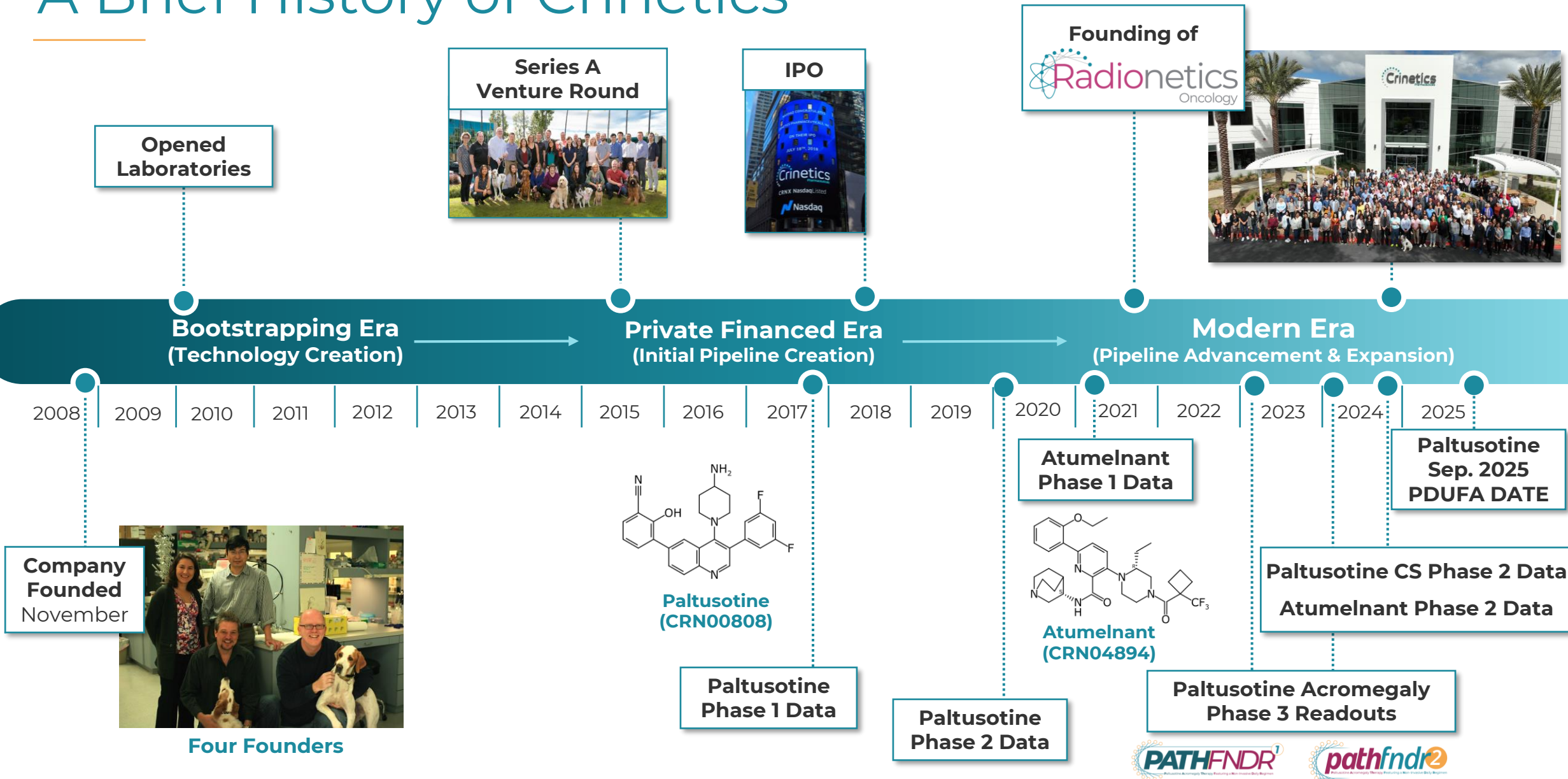
**Traci**  
Acromegaly Patient



## Our Passion for This Work Runs Deep



# A Brief History of Crinetics



# Crinetics is Well-Positioned to Advance Standards of Care With Endocrine Science



**First** anticipated commercial **launch** this year



**Deep pipeline** with **2** late-stage programs in **4** indications



**World-class R&D** capabilities, **4** candidates in preclinical



**IP rights** into 2040s



**\$1.3B** of cash, cash equivalents & investments

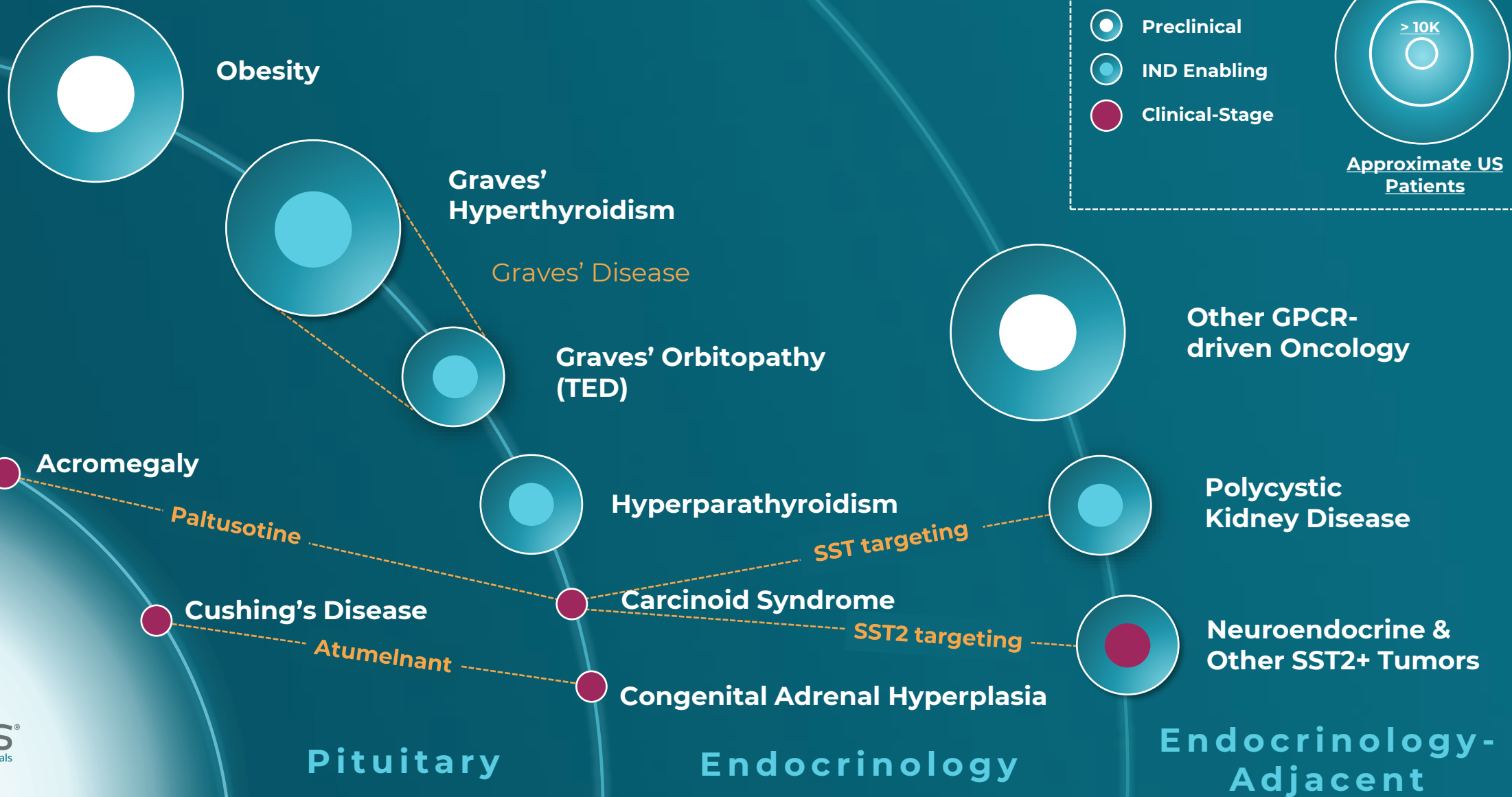


Extensive internal **endocrinology expertise**

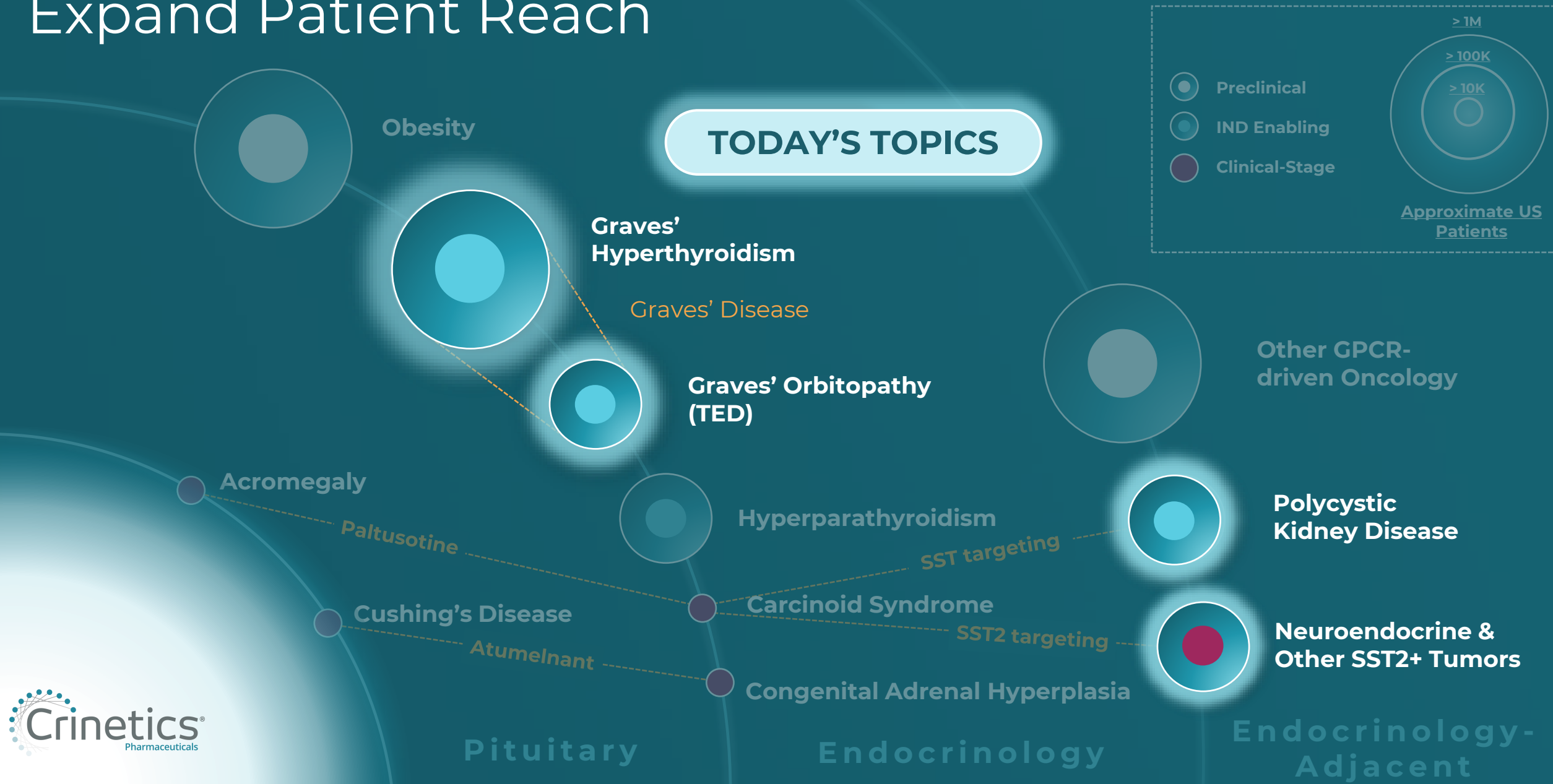


Culture dedicated to **patients** and **science**

# Exploring New Frontiers With Our Science to Expand Patient Reach



# Exploring New Frontiers With Our Science to Expand Patient Reach



# DISCOVERY OVERVIEW

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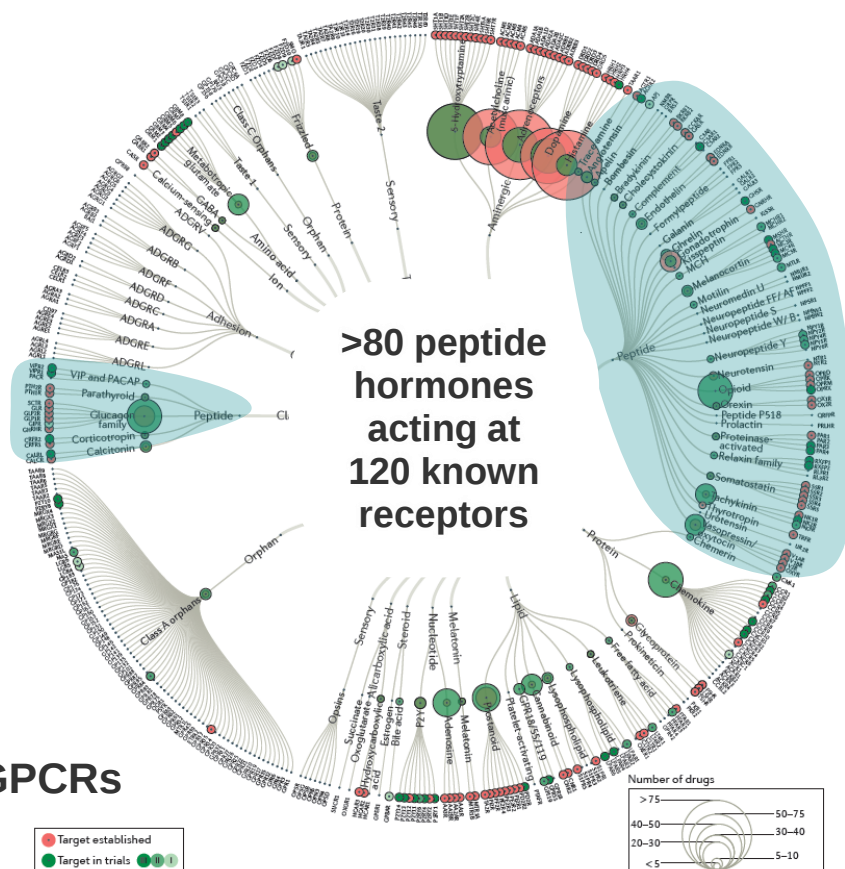
**Stephen Betz, Ph.D.**

Founder & Chief Scientific Officer



# Crinetics' Target Selection Focuses on the Intersection of Endocrinology and Peptide Hormone GPCR Pharmacology

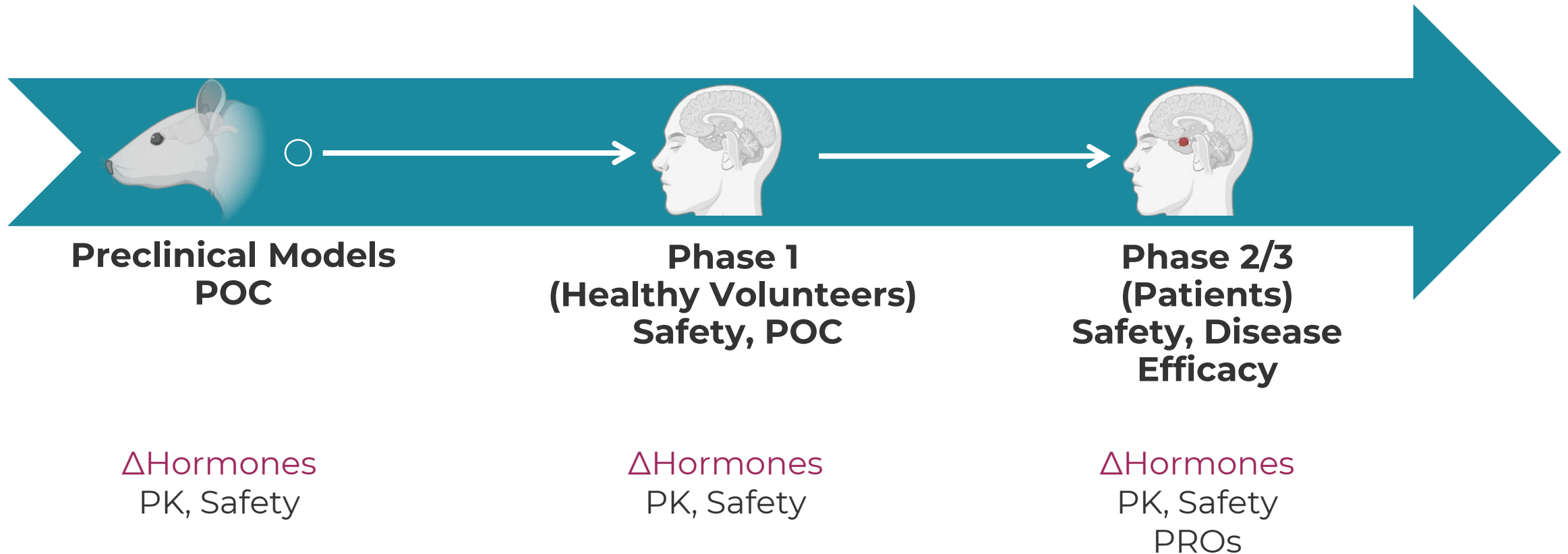
## The GPCR Superfamily



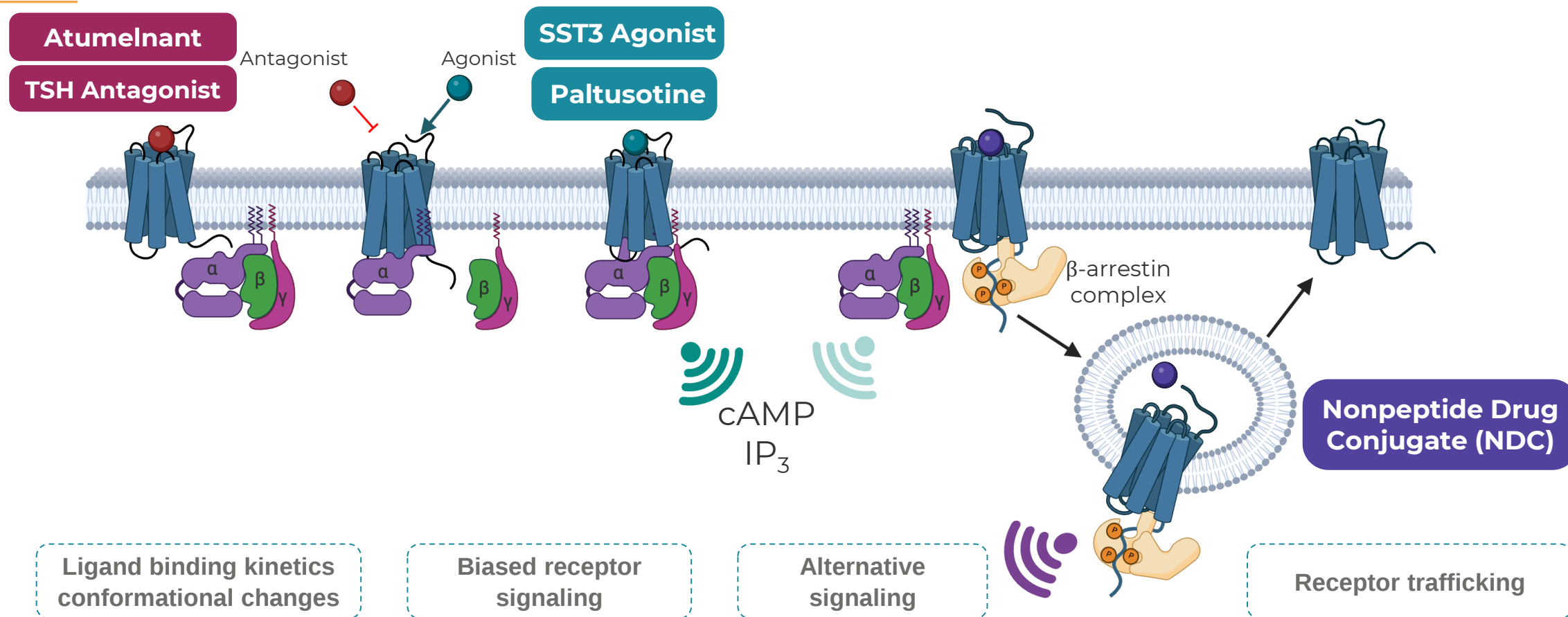
## Crinetics Current Indications

- Acromegaly
- Carcinoid Syndrome
- Congenital Adrenal Hyperplasia
- ACTH-dependent Cushing's Syndrome (ADCS)
- NETs & Other SST2+ Tumors
- Polycystic Kidney Disease
- Graves' Disease (including Graves' Hyperthyroidism and Graves' Orbitopathy)
- Hyperparathyroidism
- Obesity

# Our Strategy: Early Derisking with Biomarker Validation from Discovery through Approval

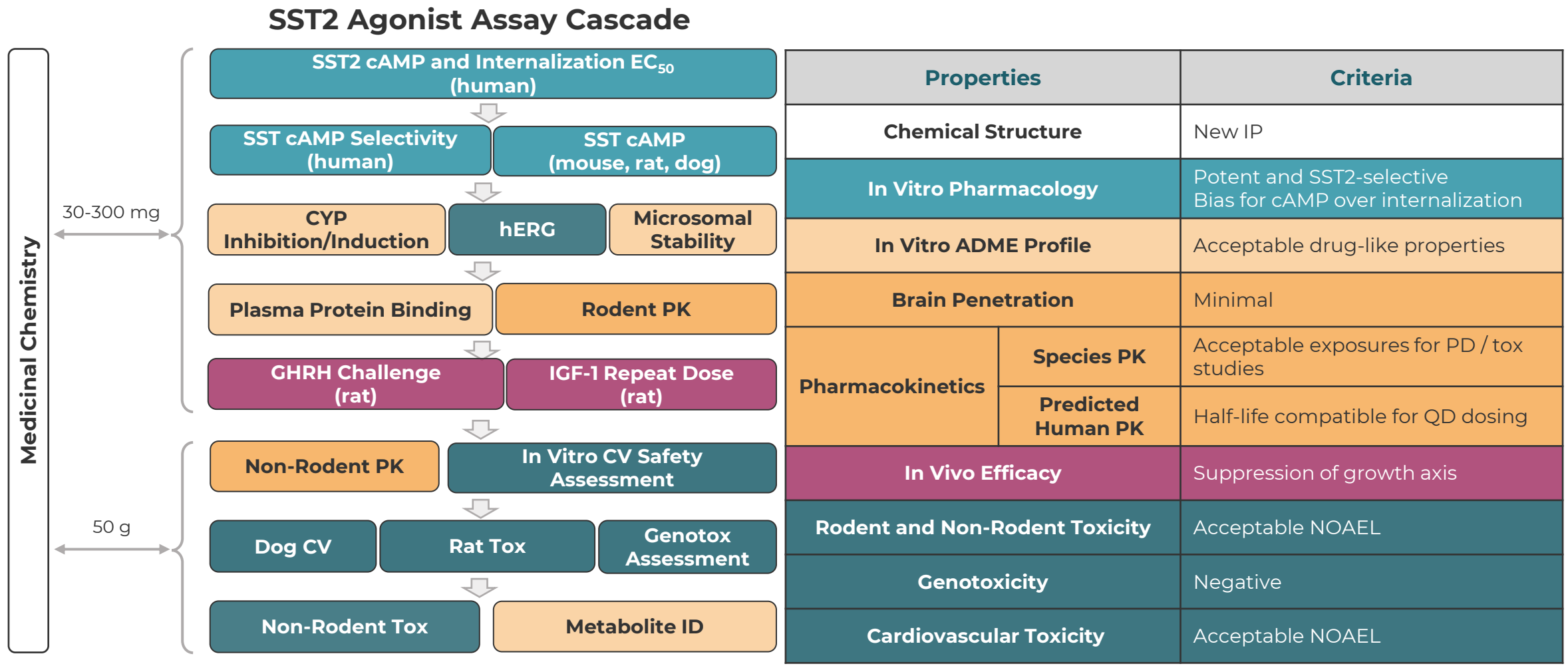


# Our Approach: Tailor Ligands to Regulate Dynamic GPCR Behaviors to Ultimately Improve Patient Outcomes



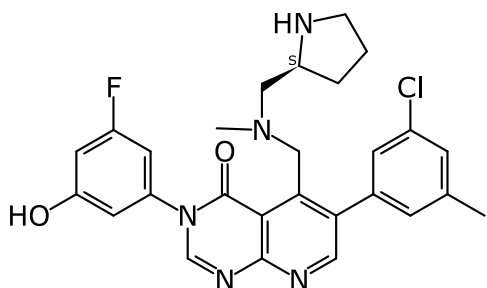
*Our understanding of complex GPCR signaling pathways enables us to develop product candidates that target specific GPCR dynamic behaviors*

# Despite Similarities, Every Assay Cascade Must Be Optimized for Receptor Specifics and Desired Drug Characteristics



# Early Leads Show the Way to Finding Clinical Class Compounds

## Early Lead

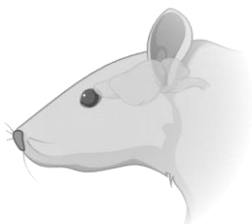
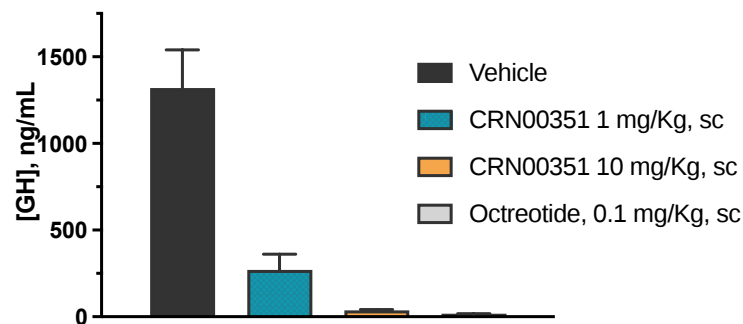


### CRN00351

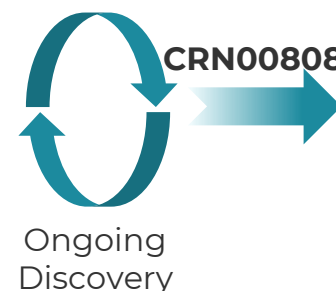
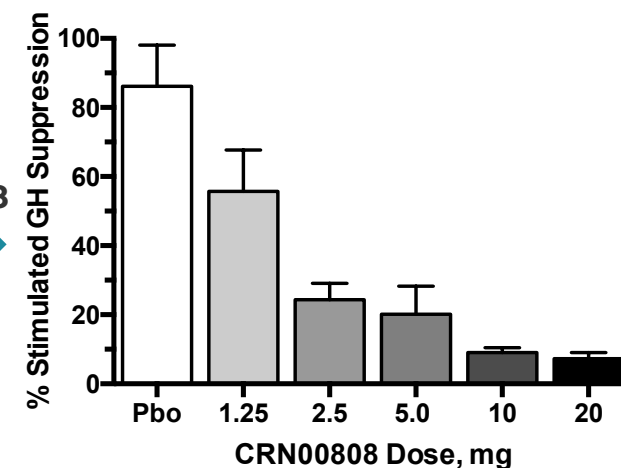
hSST2  $EC_{50}$ =0.45 nM

hSST4  $EC_{50}$ =0.47 nM

## Rat GHRH Challenge

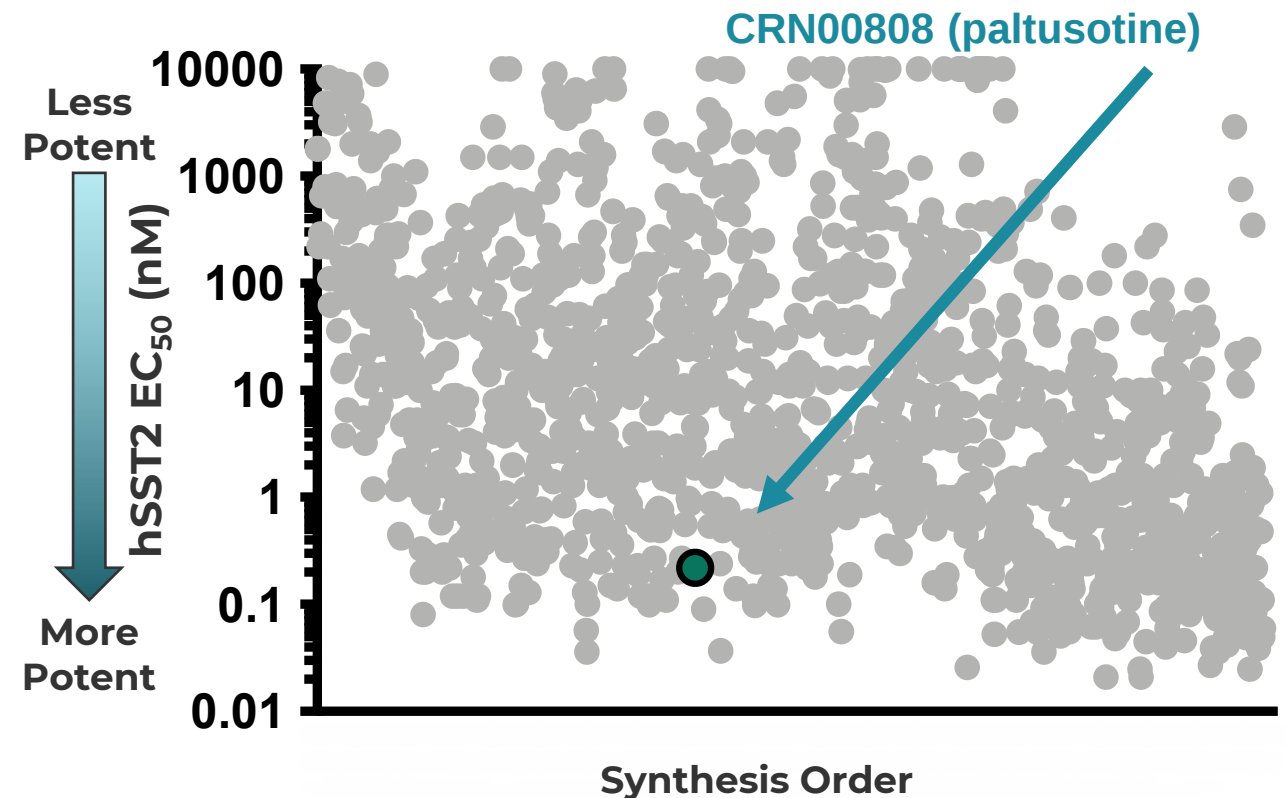
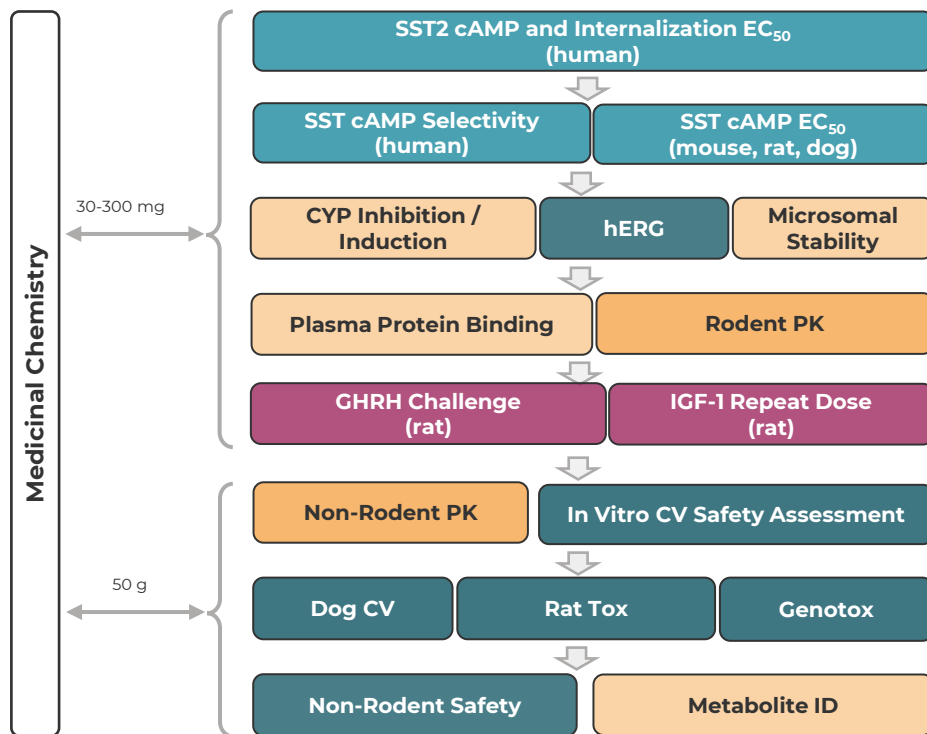


## Healthy Volunteer GHRH Challenge

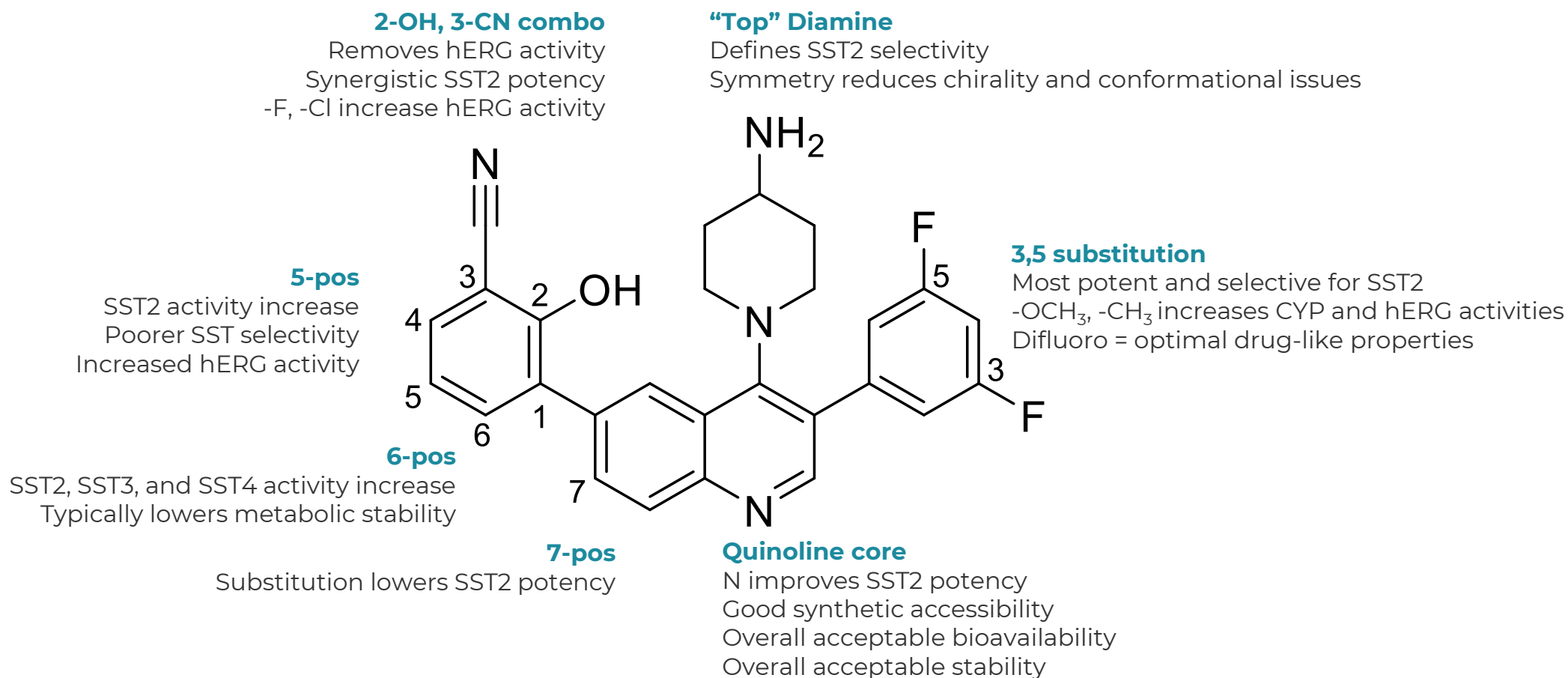


*Every molecule Crinetics moves into the clinic is designed to exceed a high bar for selectivity, drug exposure and drug-like properties*

# The Ultimate Clinical Compound Is a Balance of Multiple Inputs and Evaluations

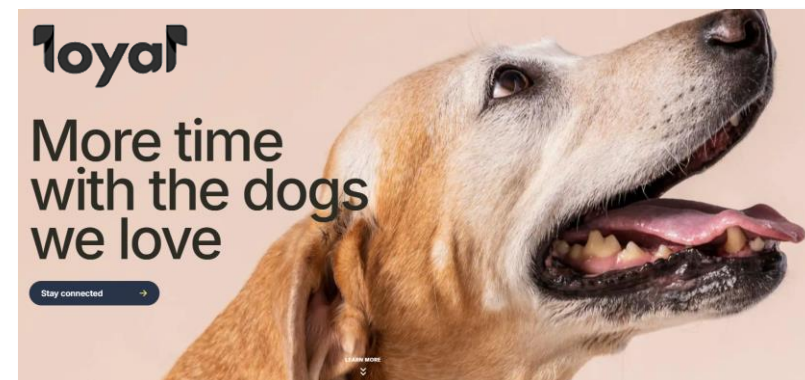
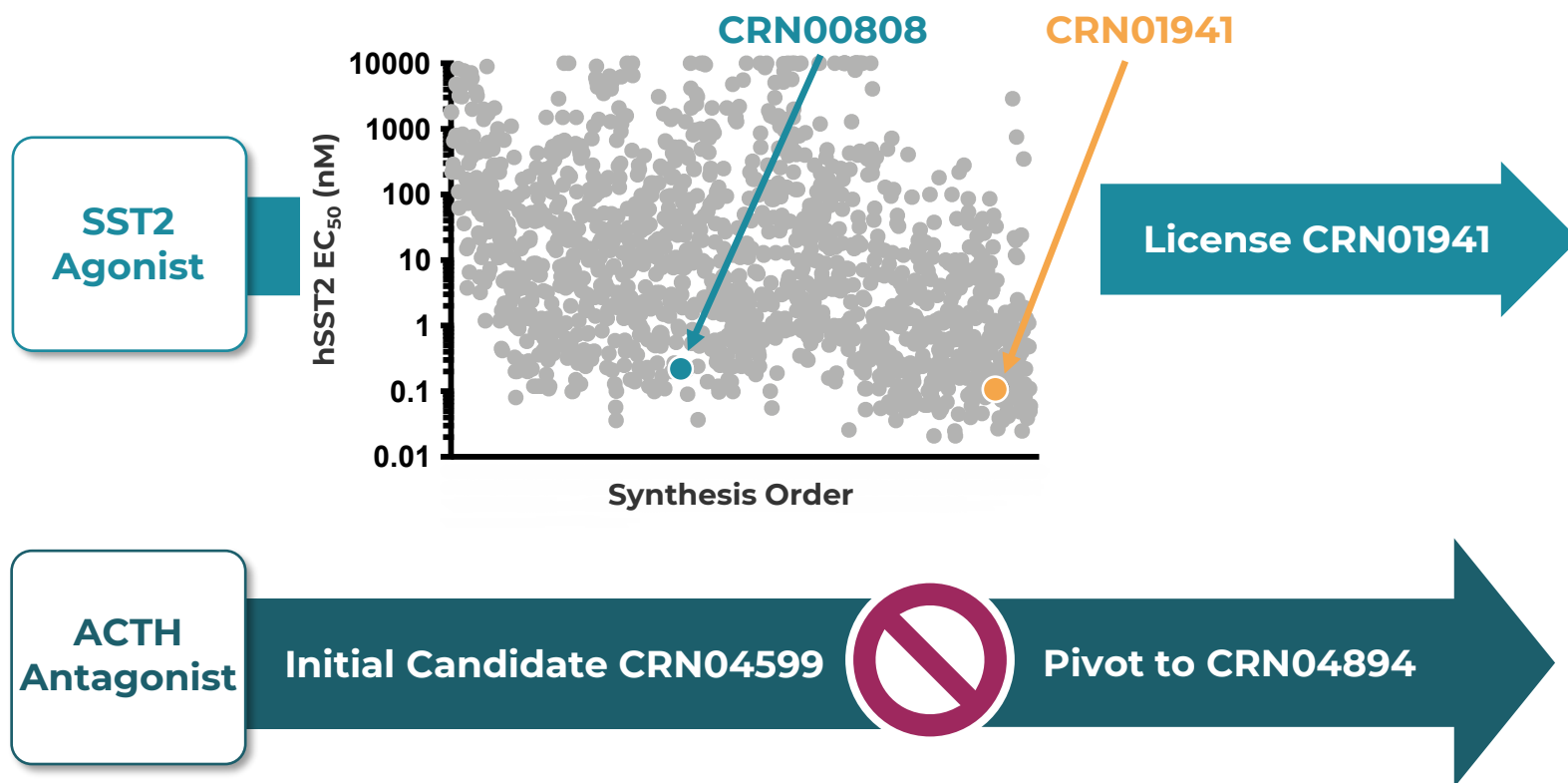


# Every Atom in Paltusotine (CRN00808) Was Optimized For Pharmacologic and Pharmaceutical Properties



# Discovery Is (Almost) Never a One-and-Done Process

## Backup Molecules Provide Insurance and Opportunity



CRINETICS ANNOUNCES POSITIVE TOPLINE RESULTS FROM PHASE 2 TRIAL OF ATUMELNANT IN CONGENITAL ADRENAL HYPERPLASIA (CAH)

*Substantial, Rapid and Sustained Statistically Significant Reductions of Key Biomarkers Achieved Across Doses, Including up to 80% Mean Reduction of Androstenedione*

*Meaningful Improvements Demonstrated in Multiple Clinical Signs and Symptoms of CAH Affecting Patient Health*

*Safety and Efficacy Data Support Initiation of Phase 3 Clinical Trial*

# Patients Play a Fundamental Role in Discovery and Development



We engage in **patient advocacy** starting in the Discovery phase



Feedback on patient journey is **incorporated into** overall **strategy and trial designs**



**Early input optimizes enrollment** and positions candidates for success to **address unmet need**



**Awareness** initiatives **build network**, develop insights, and support communities



**Acromegaly Awareness Day**  
November 1, 2019

*Patient engagement is in our DNA, with nearly two decades of relationship building that began well before our work in the clinic*

# TSHR ANTAGONIST

GRAVES' DISEASE:

Graves' Hyperthyroidism

Graves' Orbitopathy (Thyroid Eye Disease, TED)

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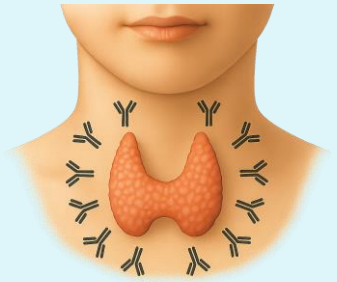
**Rick Grimes**

Global Product Leader, TSH



# Graves' Hyperthyroidism and Orbitopathy (TED) Have Significant Negative Effects on Patients

## Graves' Hyperthyroidism



- Graves' disease is one of the most common endocrine diseases, affecting **~3 million individuals in the U.S.**<sup>1</sup>
- Symptoms include irritability, tremor, fatigue, weight loss, dyspnea and heat intolerance
- Major complications include atrial fibrillation, heart failure and thyroid storm

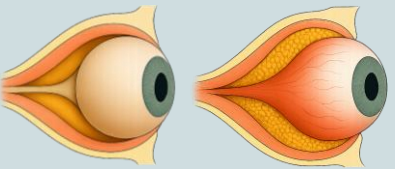


### Significant Impact on Patients

- Emotional, mental and physical fatigue
- Anxiety
- Difficulty concentrating due to “brain fog”
- Reduced performance on daily living and work activities

## Graves' Orbitopathy (TED)

Healthy Eye    TED Eye



- **~500,000 prevalent patients in the U.S.**<sup>2</sup>
- Causes inflammation and damage to the tissues around the eye, including muscles, fatty tissue, and connective tissue
- Typically follows a biphasic course: active inflammatory phase (1-3 years) followed by a chronic, fibrotic phase
- Can lead to vision loss and blindness



### Significant Impact on Patients

- Significant physical discomfort including ocular pain, double vision and proptosis
- Can lead to psychosocial distress, such as anxiety and depression
- Difficulty with daily tasks such as driving, reading and social interactions

1. [Lee et al. 2023](#)  
2. [Bartalena et al. 2020](#)

# Graves' Hyperthyroidism: Standard of Care Has Been Stagnant for Decades and Has Significant Limitations

**ATDs have become the highly preferred 1L treatment in the US (~90%) due to risks associated with ablative therapies**

## Antithyroid Drugs (ATDs)

### MOA

- Inhibits thyroid hormone synthesis in the thyroid gland

### Limitations

- **Does not prevent or treat Graves' Orbitopathy**
  - 30-50% of Graves' patients develop TED<sup>1</sup>
  - Typically develop TED within 18 months of onset of Graves' Hyperthyroidism
- Potential for **serious side effects** including **liver injury (~3%)<sup>2</sup>** and **agranulocytosis (~0.3%)<sup>3</sup>**
- Other adverse effects including Itching, rash, hives, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting in up to 13% of patients<sup>2</sup>

## Ablative Therapy

### MOA

- Ablation of thyroid function, either with
  - **Radioactive iodine (RAI)**, which destroys the thyroid cells
  - **Thyroidectomy** (surgical thyroid removal)

### Limitations

- **Permanent hypothyroidism** and **lifelong thyroid hormone replacement** therapy
- Thyroidectomy **risks parathyroid gland and laryngeal nerve damage**
- RAI has **risk of radiation thyroiditis** or **secondary malignancies**
- RAI has **increased risk of incidence or exacerbation of TED**

1. [Chin et al. 2020](#)  
2. [Sundaresh et al. 2013](#)  
3. [Watanabe et al. 2012](#)

# Graves' Orbitopathy (TED): Anti-IGF-1R Has Changed the Treatment Paradigm but There is a Need for a Safer Therapy

## Teprotumumab (anti-IGF-1R mAb)

- Inhibition of IGF-1R improves proptosis associated with TED
- Teprotumumab reduces proptosis with up to 80% response<sup>1</sup> but **many experience relapse** (>30%)<sup>2</sup>
- Risks of therapy include:
  - **On target risk of hearing impairment (10-20%)<sup>3,4</sup> and hyperglycemia (10%)<sup>3,5</sup>**
  - **Other safety risks** including muscle spasms (32%), alopecia (15%), nausea (12%) and fatigue (10%)<sup>6</sup>
- Requires burdensome IV dosing in an infusion center
- **Not suitable for all patients** – precautions for those with inflammatory bowel disease, diabetes and pre-existing hearing conditions

1. [Douglas et al. 2020](#)

2. [Couch 2022](#)

3. [Kahaly et al. 2021](#)

4. [Douglas et al. 2023](#)

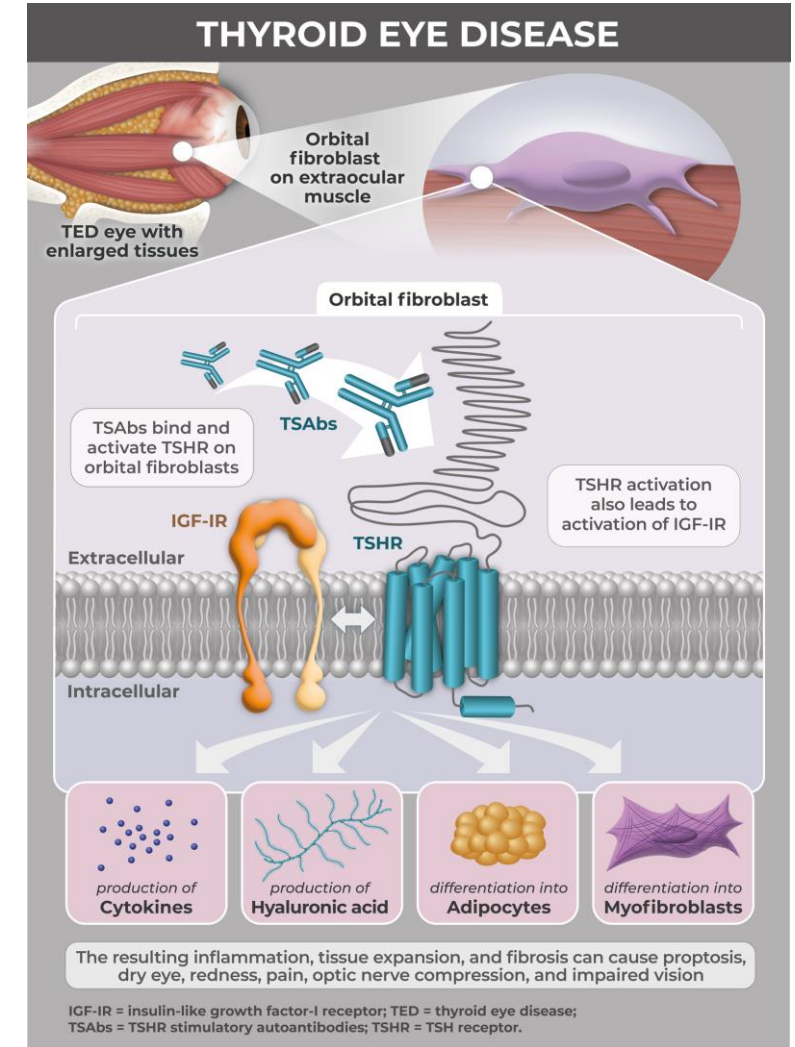
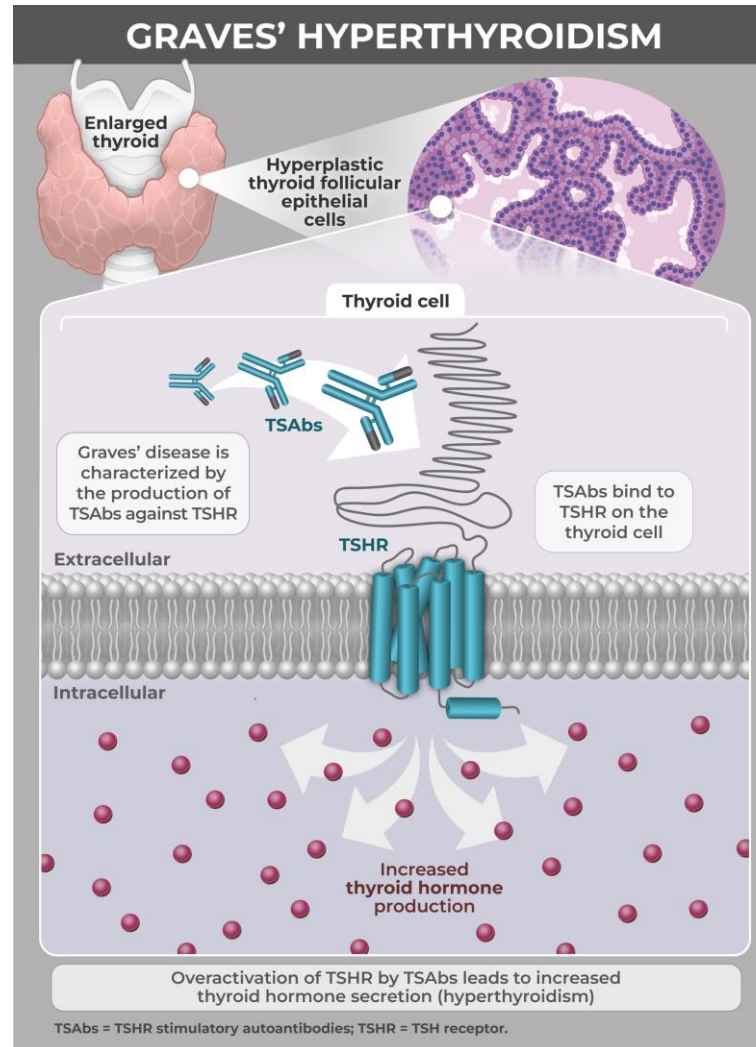
5. [Smith et al. 2024](#)

6. [Teprotumumab FDA briefing document Dec. 13, 2019](#)

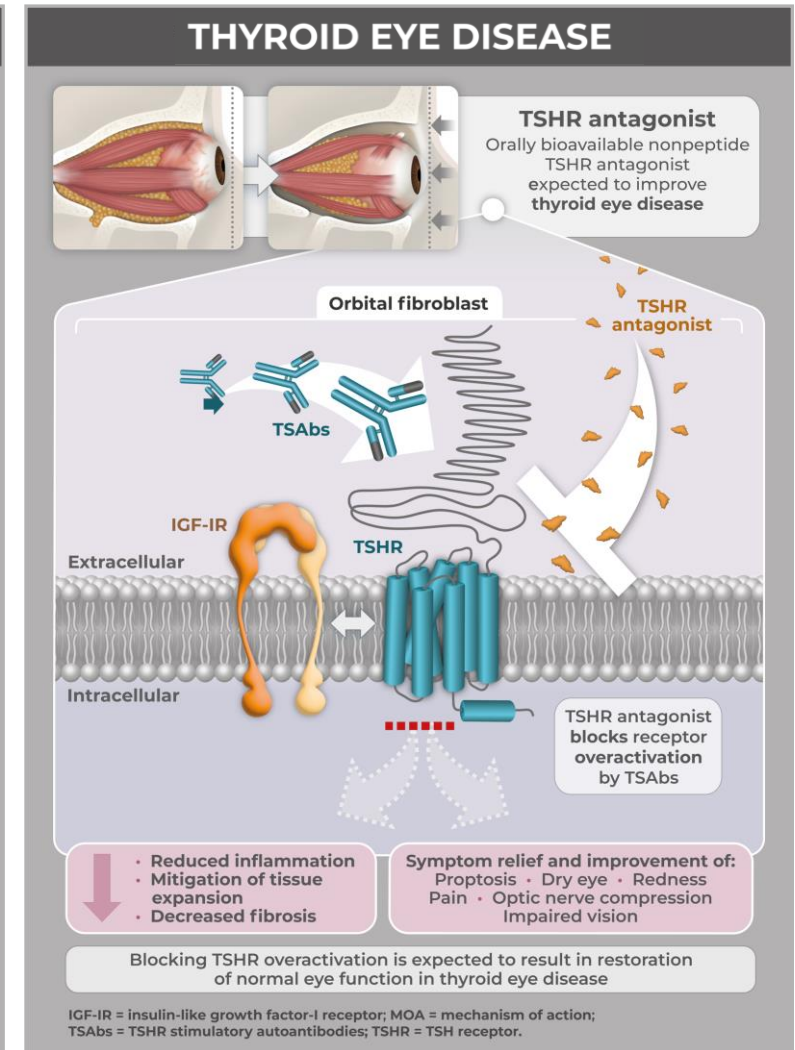
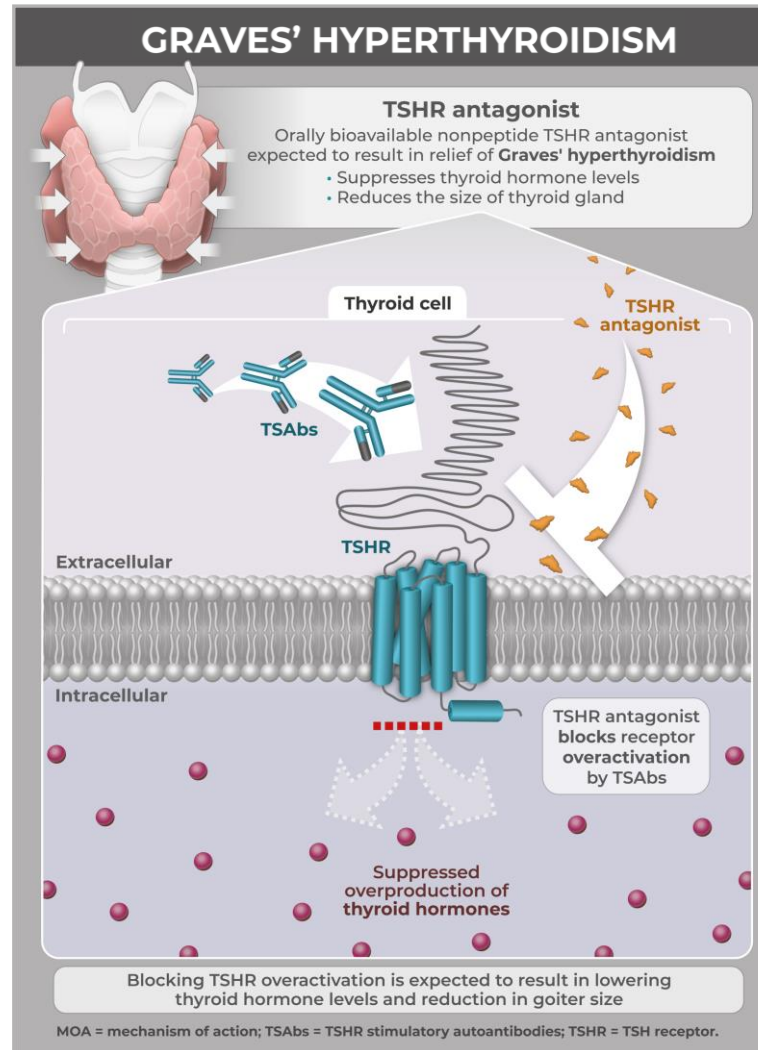
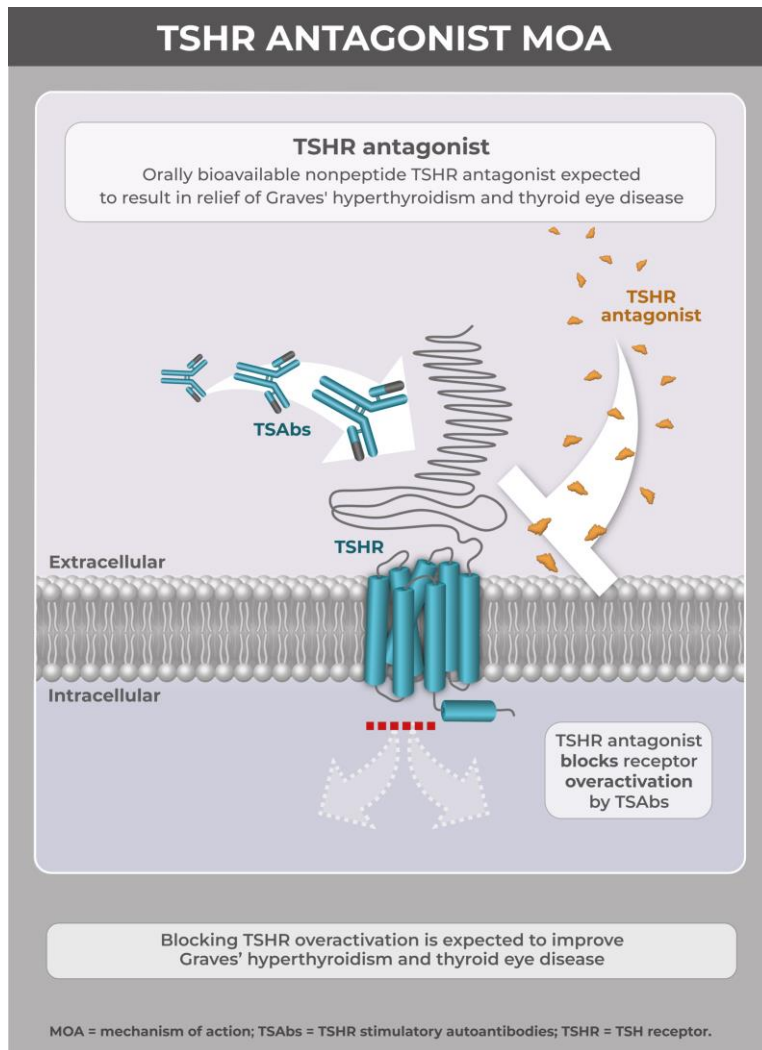
# The Core Driver of Both Graves' Hyperthyroidism and Orbitopathy (TED) is Over-Stimulation of TSHR by TSHR Stimulating Auto-Antibodies (TSAbs)

Graves' Disease has two major manifestations:

- Hyperthyroidism
- Orbitopathy (also known as Thyroid Eye Disease or TED)



# TSHR Antagonism: A Targeted, Novel Mechanism to Treat Both Major Manifestations of Graves' Disease



# Crinetics Has Developed Potent and Selective Small Molecule, TSH Receptor Antagonists

## CRNX TSHR Antagonists

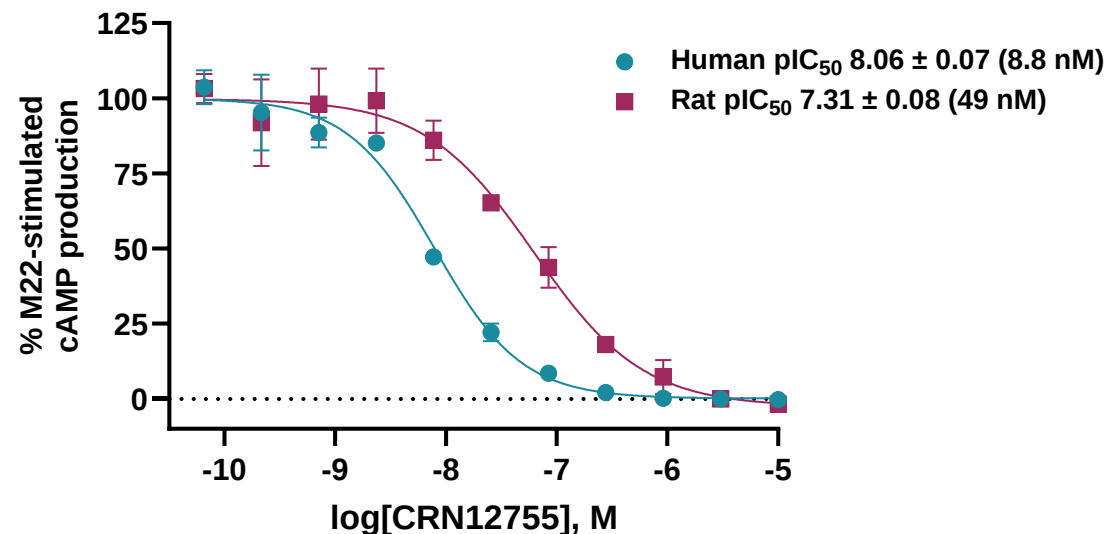
- Structurally diverse
- Potent and selective for TSHR
- Good ADME properties

## CRN12755

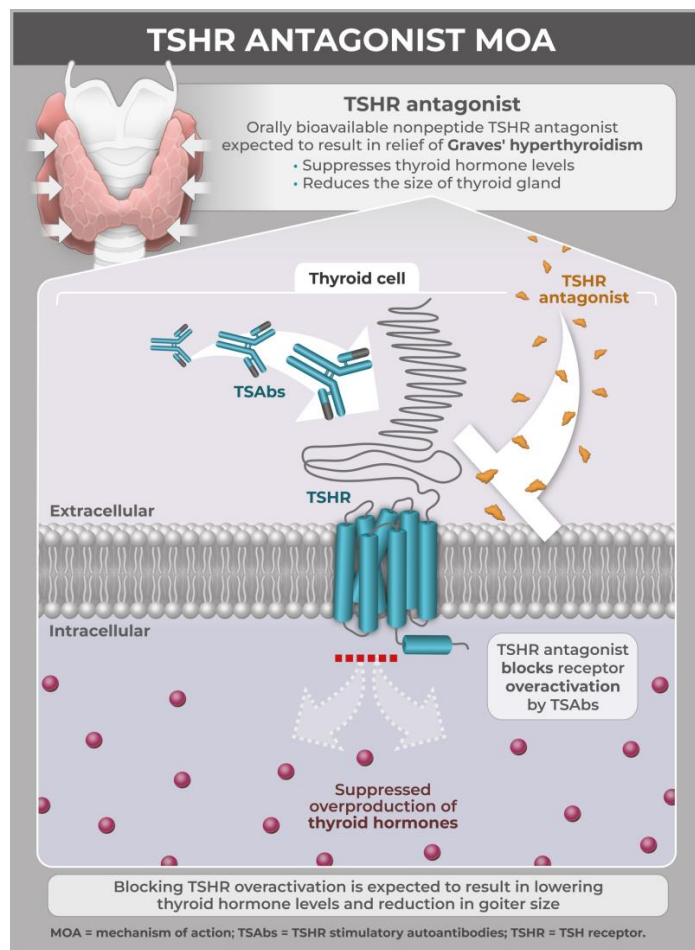
### (leading development candidate)

- Predicted human PK to support QD dosing
- Efficacious in Graves' Hyperthyroidism rat model
- Inhibits TSAb stimulation in human Graves' patient orbital fibroblasts
- IND-enabling safety studies in progress

## CRN12755 Is Potent Functional Antagonist of Human TSHR

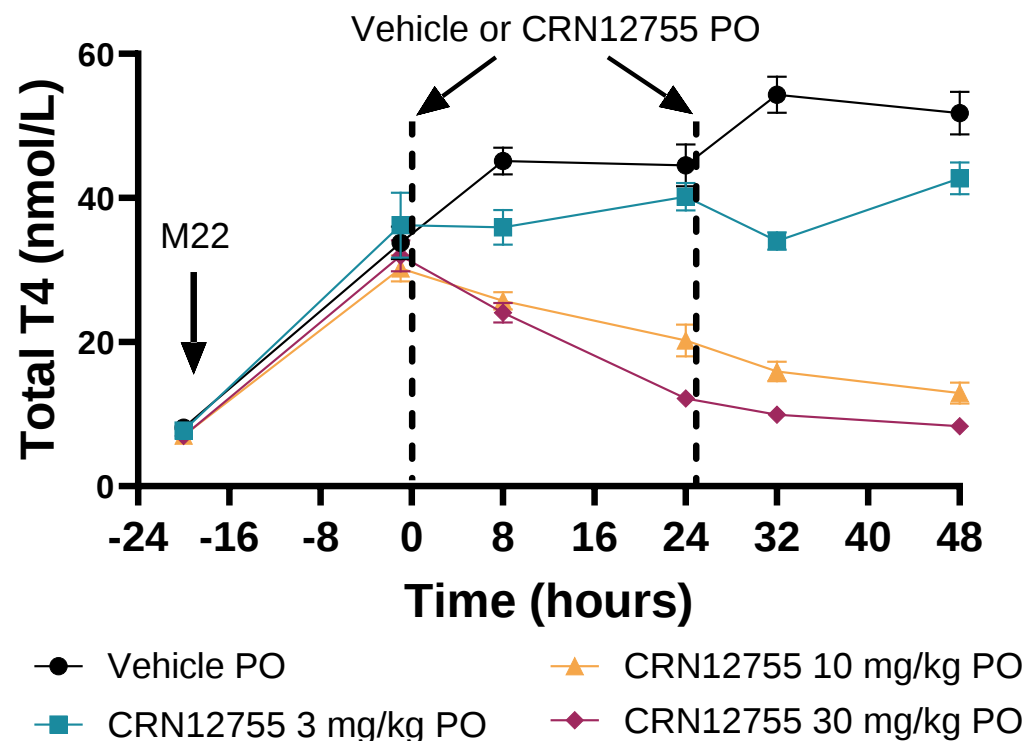


# Graves' Hyperthyroidism: CRN12755, a TSHR Antagonist, Reduced Thyroid Hormone Levels in a Stimulated Rat Hyperthyroidism Model

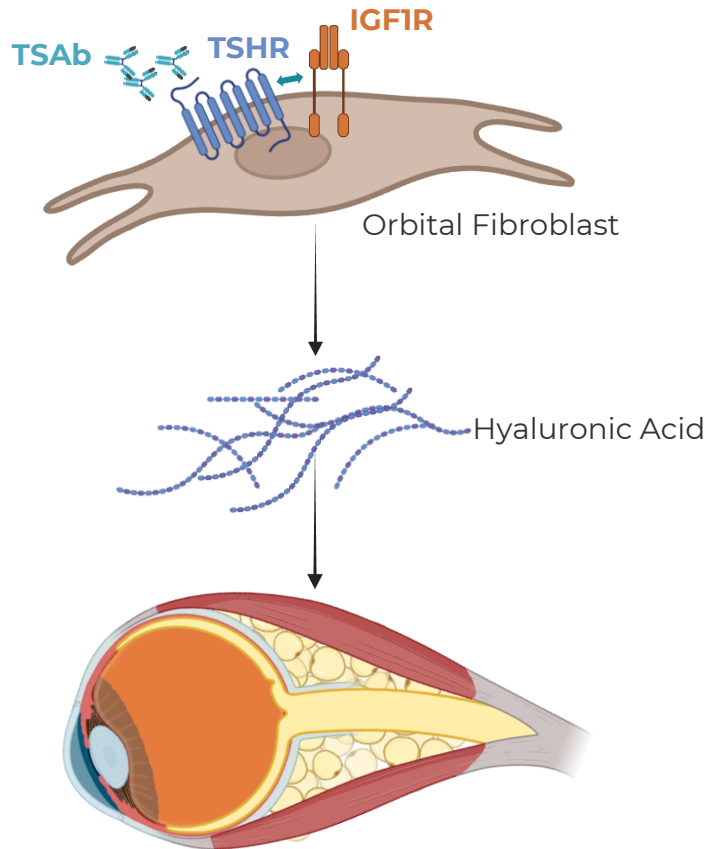


## RAT HYPERTHYROIDISM MODEL

Oral administration of CRN12755 dose dependently reduced TSAb (M22) stimulated thyroid hormone (T4) levels



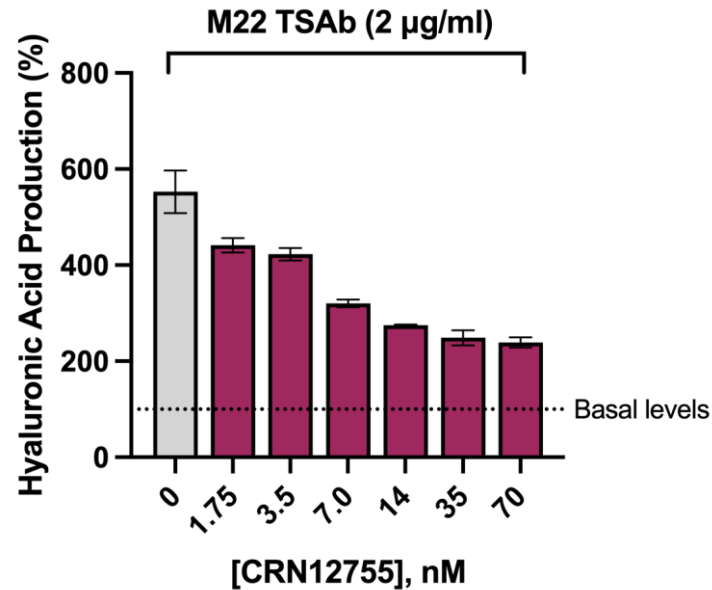
# Graves' Orbitopathy (TED): CRN12755 Suppressed TSAb-Stimulated Hyaluronic Acid Production in TED Patient-Derived GOFs



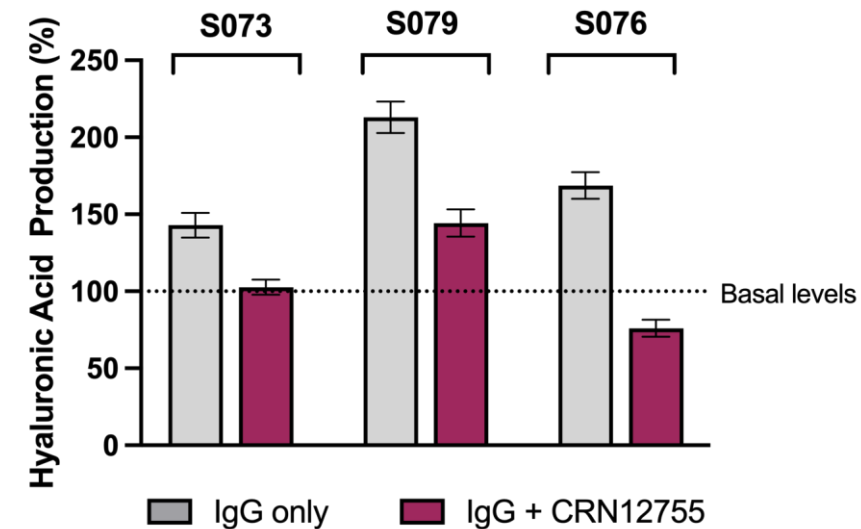
Hyaluronic acid attracts and binds to water, increasing the volume of orbital tissue

Graves' orbital fibroblasts (GOFs) are obtained from TED patients undergoing orbital decompression surgery and differentiated into orbital adipocytes

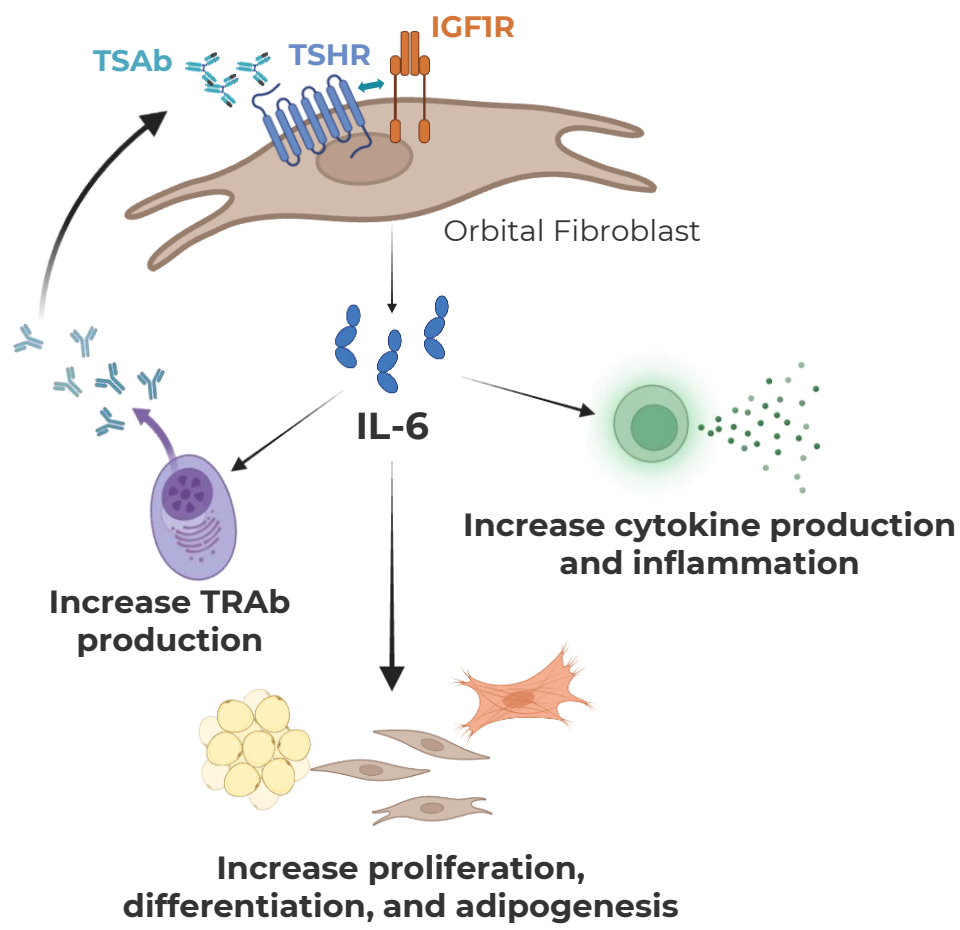
**Dose Response Demonstrated in Model with M22 Antibody Stimulation**



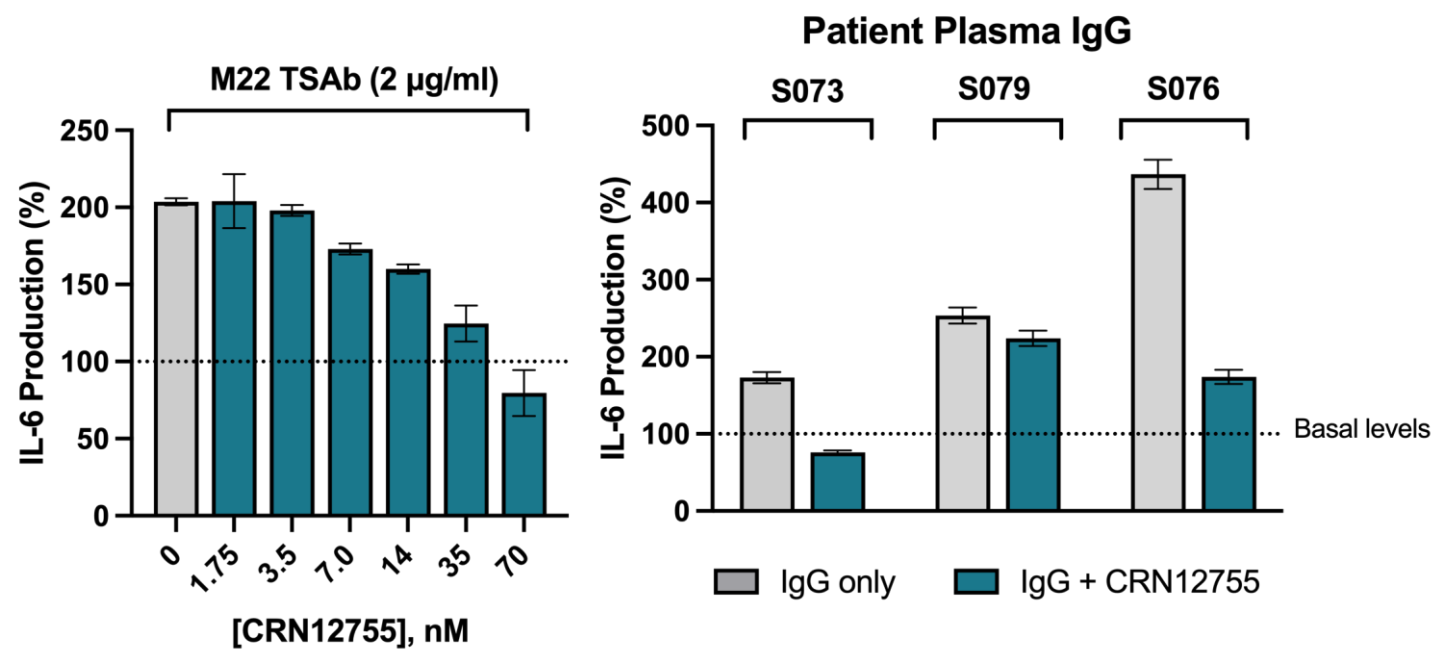
**Patient Plasma IgG**



# Graves' Orbitopathy (TED): CRN12755 Suppressed TSAb-Stimulated Production of IL-6 in TED Patient-Derived Orbital Adipocytes



Graves Orbital Fibroblasts (GOFs) from TED patients are differentiated into orbital adipocytes and stimulated with TSABs



Fowler, M. (2025)

# **TSHR Antagonist:** Has Potential to Be a Single, Oral Therapy to Treat Graves' Hyperthyroidism and Treat/Prevent Orbitopathy (TED)

## Product Vision

### Graves' Hyperthyroidism

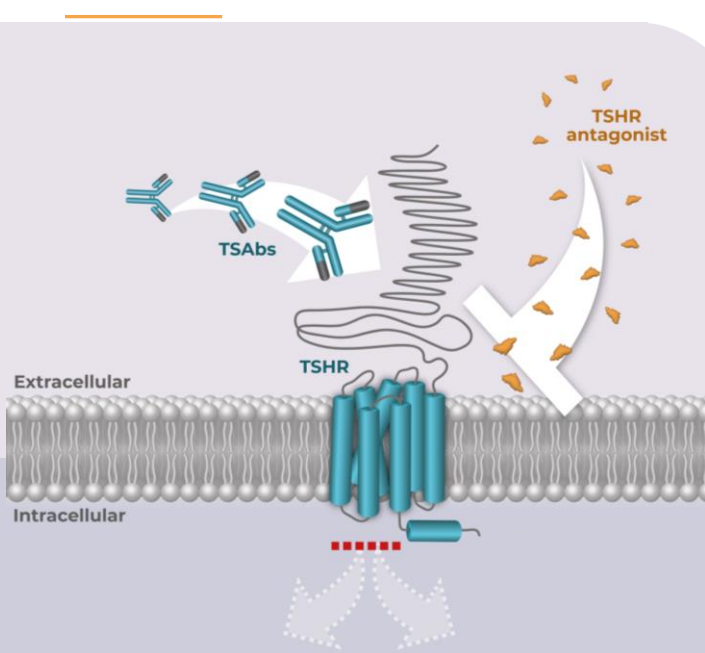
Prevent  
Orbitopathy

- Oral, once daily
- Rapid control of hyperthyroidism and symptoms
- Simultaneous treatment and prevention of orbitopathy
- No risks associated with ATDs
- Thyroid preservation

### Graves' Orbitopathy (TED)

- Oral, once daily
- Equivalent or better efficacy than approved IGF-1R mAb
- Improved safety
  - No hearing impairment or hyperglycemia
  - Enabling a more durable treatment

# A TSHR Antagonist Has Potential Advantages Over Emerging New Therapies



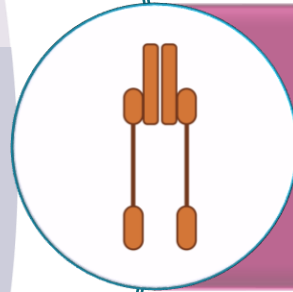
## TSHR Antagonist Product Vision

A single, oral therapy to treat Graves' Hyperthyroidism and treat/prevent Graves' Orbitopathy



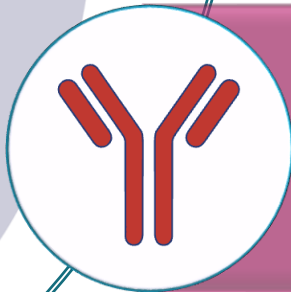
### TSHR Antagonist Potential Attributes

- Oral, once daily
- Rapid control of hyperthyroidism with thyroid preservation
- Simultaneous treatment and prevention of orbitopathy
- No adverse effects of ATDs or anti-IGF-1R and no non-specific immunomodulation



### 2<sup>nd</sup> Generation IGF-1R Inhibitors (SC or oral)

- Treat TED only
- Early data suggest subcutaneous are more efficacious than oral
- On-target side effects remain a concern (full data still pending)



### Anti-FcRn mAbs & Small Molecule Bispecific Degraders

- Reduce levels of TSABs by promoting degradation
- Broad IgG degradation, not TSAb specific
- May require large reductions in IgG (>70%)
- High dose, once weekly subcutaneous injections

# Large Patient Population in the US in Both Graves' Hyperthyroidism and Orbitopathy (TED) with High Unmet Need

## GRAVES' HYPERTHYROIDISM

**>3M prevalent patients<sup>1</sup> \***

**Up to ~1.2M with active Graves' hyperthyroidism<sup>2</sup>**

**Addressable patient population**

**up to ~170k incident<sup>3</sup>**

## GRAVES' ORBITOPATHY (TED)

**~500,000 prevalent patients<sup>4</sup> \***

**~30k incident<sup>4,5</sup>**

**~325k Mild  
(55-75%)**

**~150k  
Moderate-to-severe  
(20-40%)<sup>6,7</sup>**

**~25k Sight-threatening  
(<10%)**

**Addressable patient population**

**~9k moderate to severe incident**

\*Theoretical prevalence

1. [Lee et al. 2023](#)  
2. [Hallowell et al. 2002](#)  
3. [Smith et al. 2016](#)  
4. [Bartalena et al. 2020](#)

5. [Bartley et al. 1994](#)  
6. [Dosiou et al. 2021](#)  
7. [Muralidhar et al. 2020](#)

# Next Steps for the TSH Antagonist Program



**ENDO 2025:  
Poster  
Presentation**



**IND Submission**



**Phase 1 Healthy  
Volunteer Study**

***Early Proof-of-Concept in Phase 1 with Thyroid Biomarkers (TSH, T3, and T4)***

# SST3 AGONIST

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE  
(ADPKD)

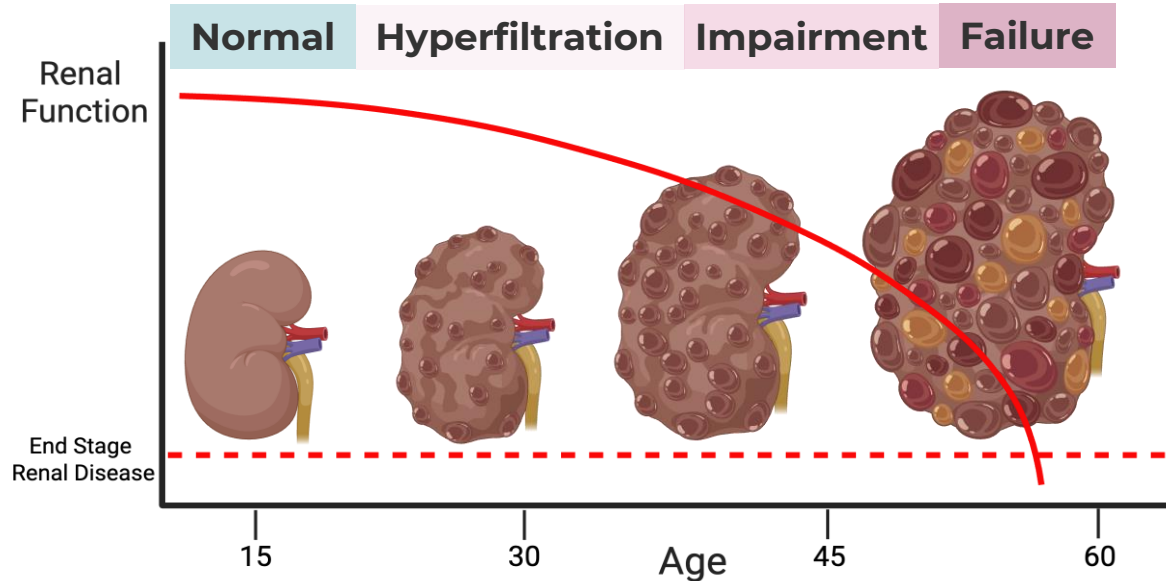
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**Stephen Betz, Ph.D.**

Founder & Chief Scientific Officer



# Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a Genetic Disease That Significantly Impacts Quality of Life



## Most common inherited kidney disorder (~145K diagnosed patients in the US)

- Abnormal primary cilia function triggers cystogenesis, fluid-filled cysts that gradually enlarge

## Leads to kidney failure and dysfunction

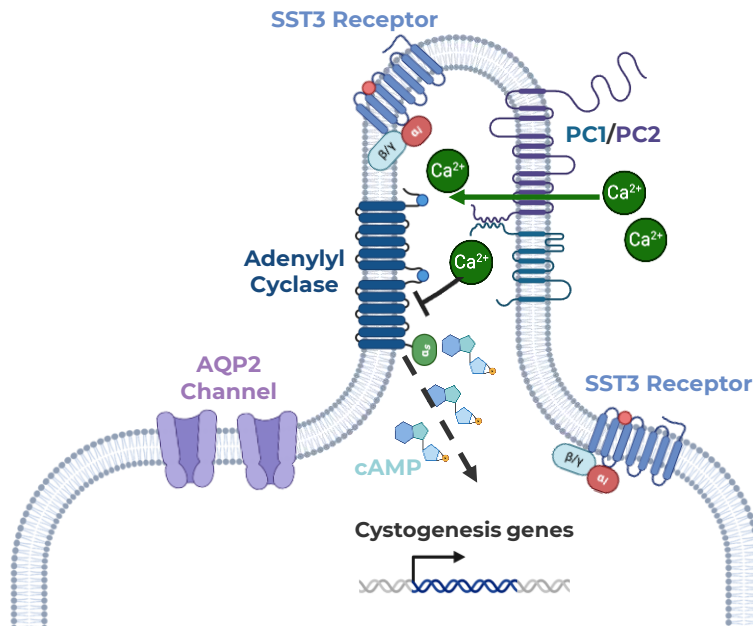
- 50% of patients develop end stage kidney disease (ESKD), requiring dialysis or kidney transplant

## Tolvaptan (current standard-of-care) only used by <10% of patients:

- Modest efficacy
- Boxed Warning: Acute liver injury
- Key adverse effects (mechanism-dependent):
  - **Increased frequency of urination**
  - Thirst
  - Dehydration

# ADPKD is a Disease of Disrupted $\text{Ca}^{2+}$ and cAMP Ciliary Signaling

## Healthy Human Kidney

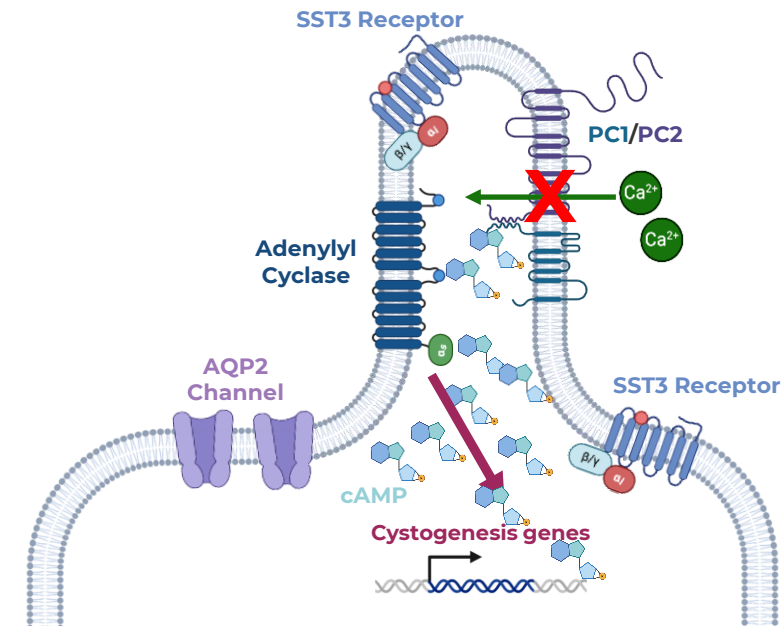


PKD1 enables ciliary  **$\text{Ca}^{2+}$  influx**

- Inhibits adenylyl cyclase and reduces cAMP

**Low ciliary cAMP levels** → **No cystogenic signal**

## ADPKD Patient Kidney

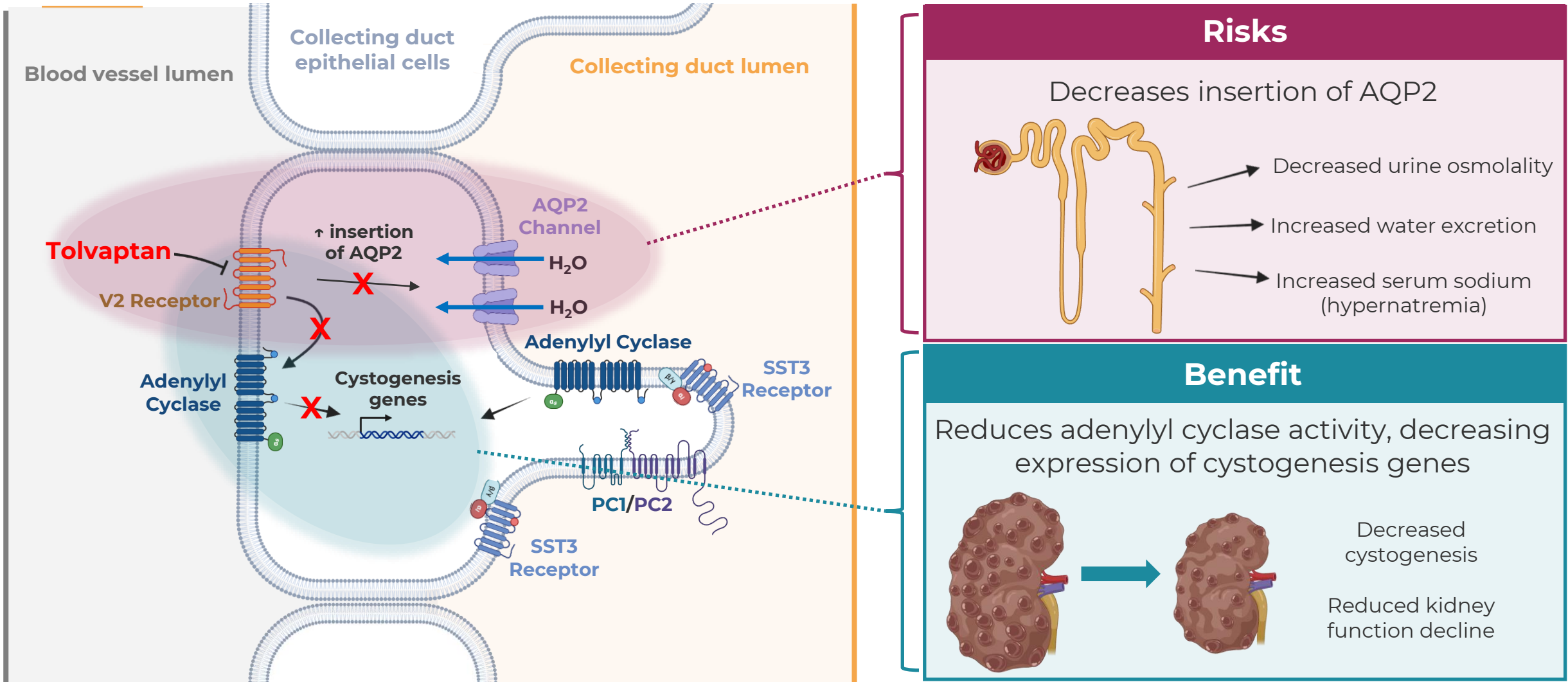


Calcium unable to enter cell to reduce cAMP

**High ciliary cAMP levels** → **Cystogenic genes induced**

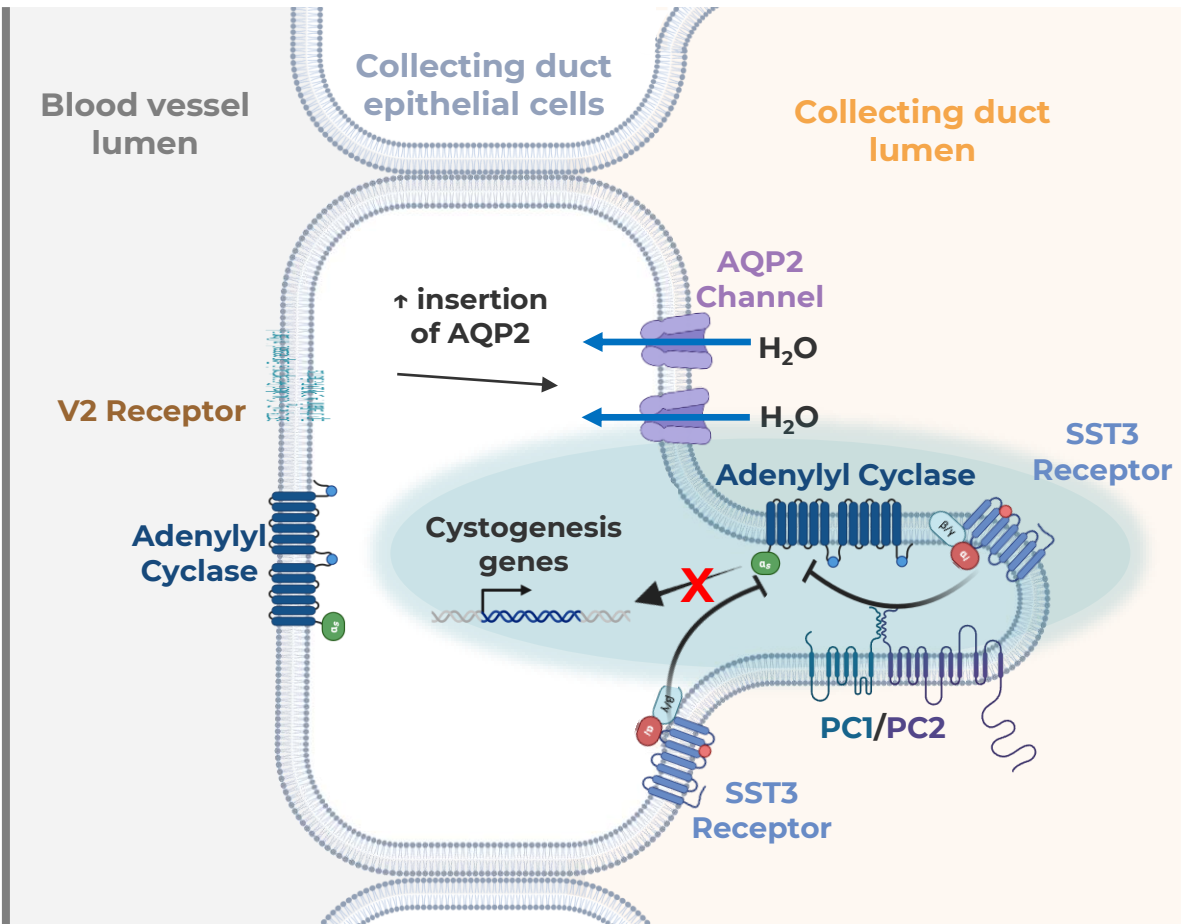
**Hypothesis: Reducing ciliary cAMP levels is a novel approach for reducing cystogenesis**

# Tolvaptan Improves Kidney Function in ADPKD, but Causes Increased Urination and Hypernatremia

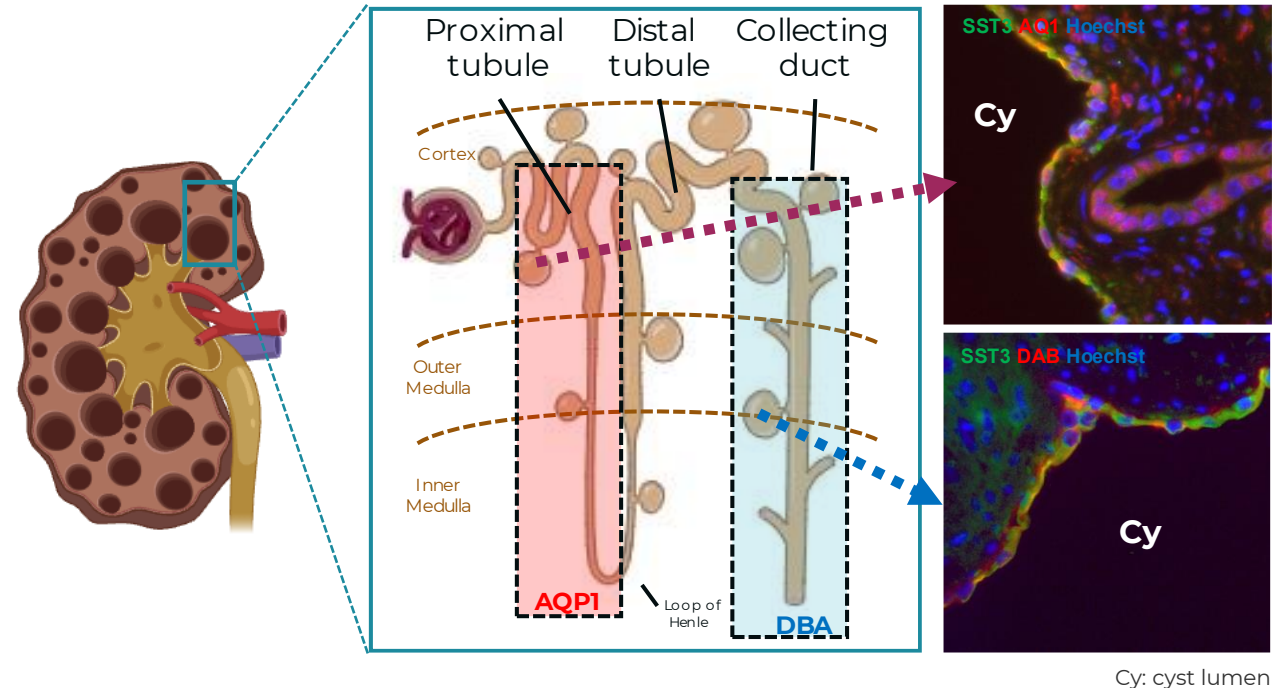


# SST3, a $G_{\alpha i}$ -Coupled Receptor, is Expressed in Renal Epithelia in ADPKD Patients

Activation of SST3 localized in cilia and apical membrane of cyst-lining cells decreases cAMP and cystogenesis



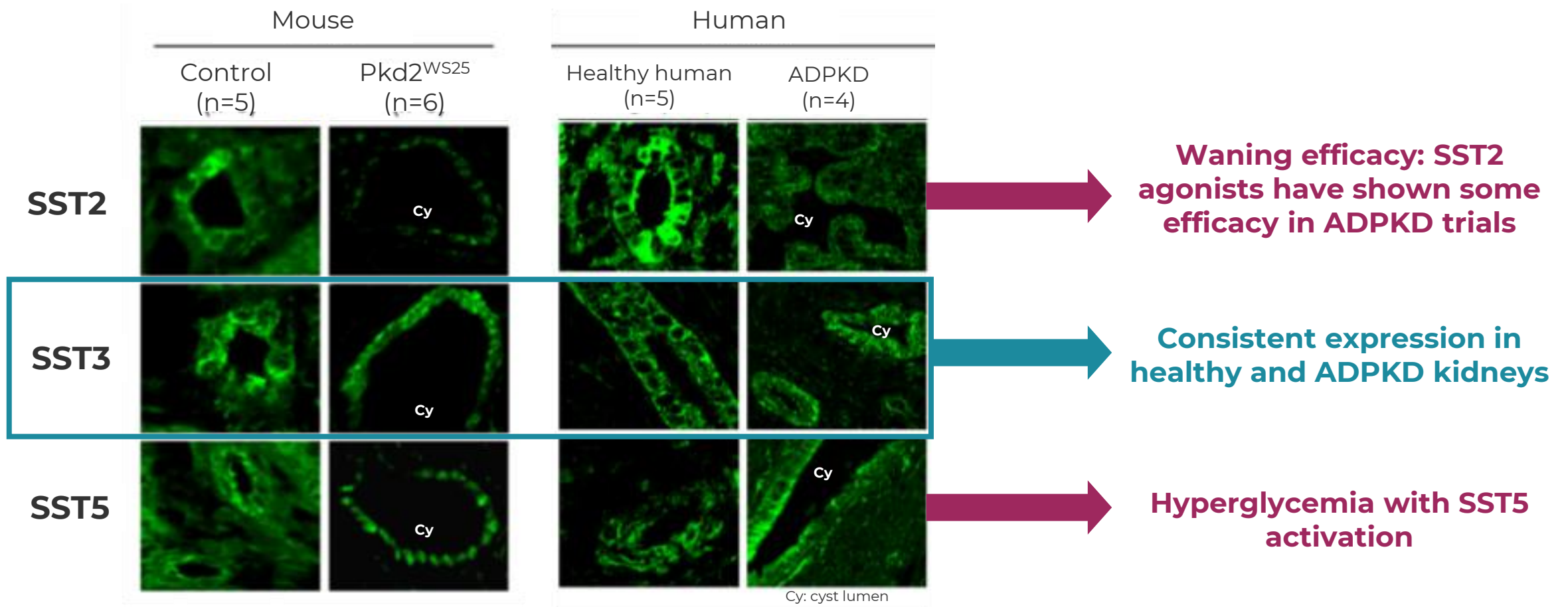
SST3 is expressed in cysts emerging from both proximal tubules and collecting ducts



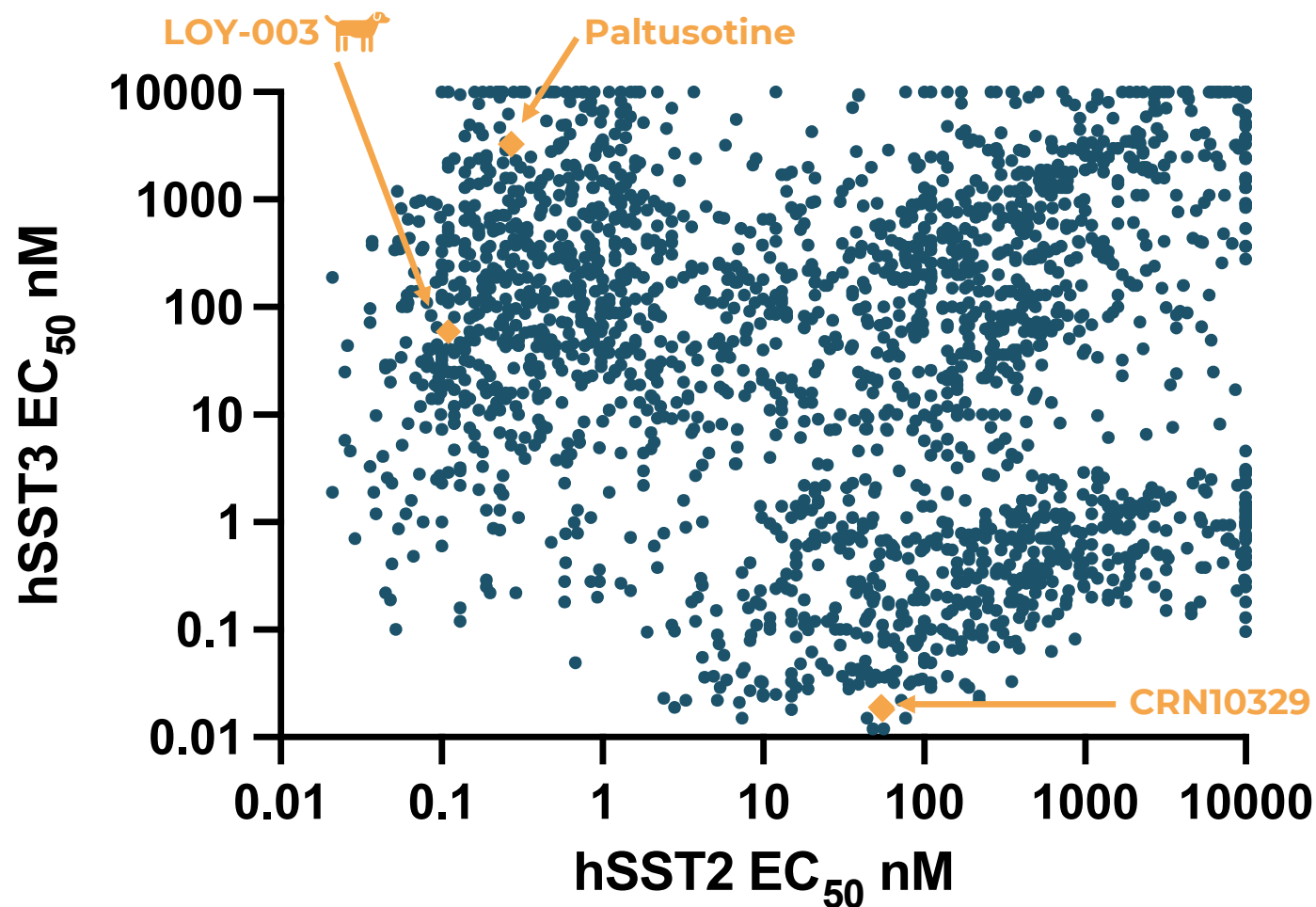
- Tolvaptan acts only on cysts originating from collecting duct
- **SST3 agonist should impact expansion of cysts originating from tubules and collecting duct**

# SST3 Agonism Represents an Effective Somatostatin-Targeted Strategy in ADPKD

**SST3 is highly and consistently expressed in cyst-lining cells in ADPKD**



# Crinetics Has Developed Potent and Selective SST3 Small Molecule Agonists



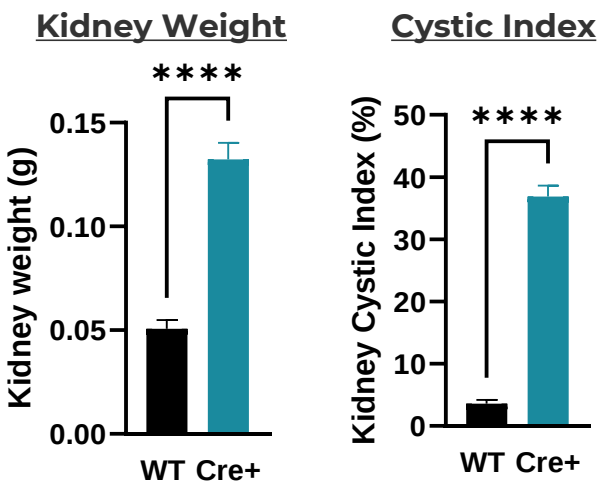
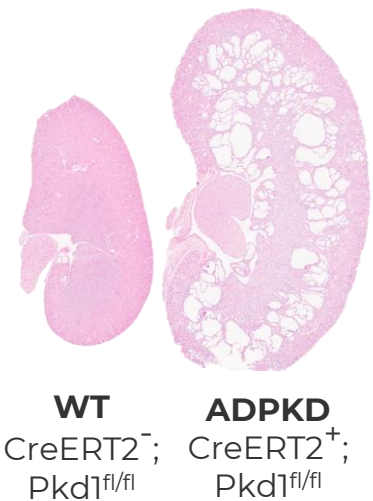
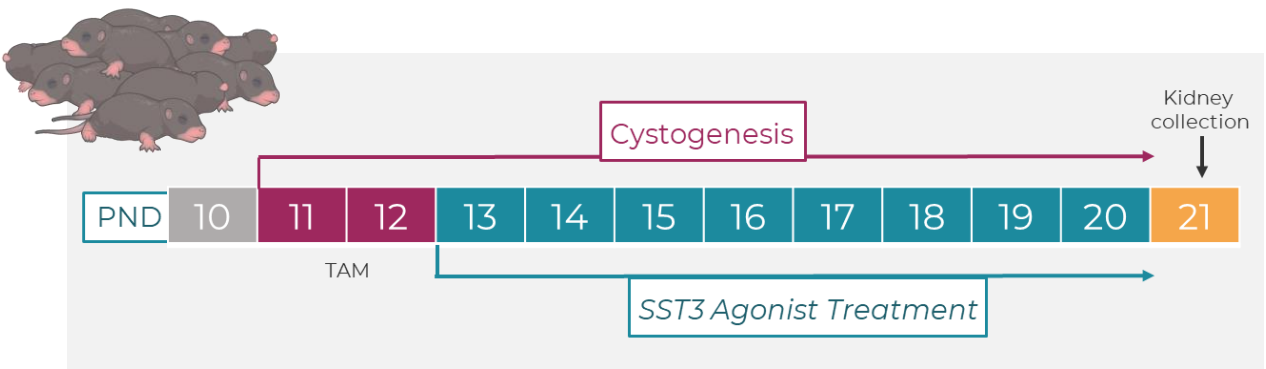
## CRNX SST3 Agonists

- Structurally diverse
- Potent and selective at hSST3
- Good ADME properties

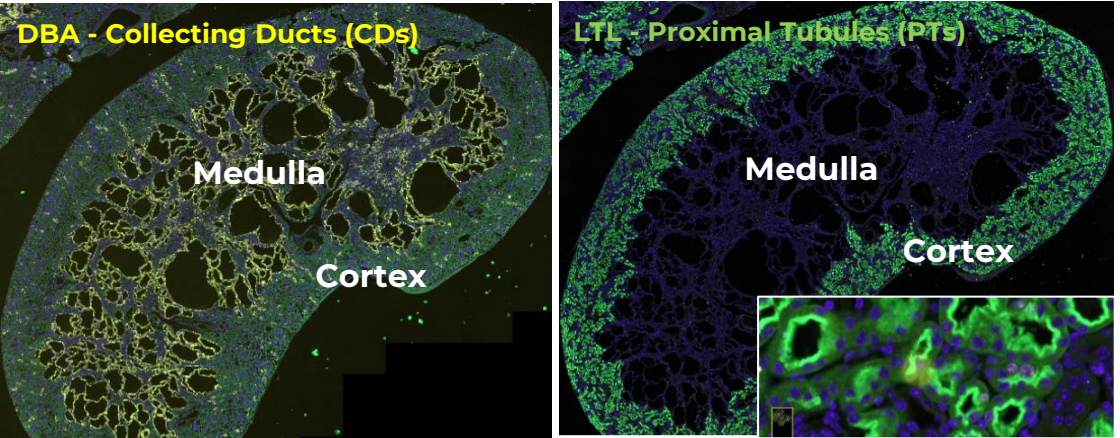
## CRN10329 (Leading Development Candidate)

- Predicted human PK supports QD dosing
- Efficacious in ADPKD mouse model
- IND-enabling safety studies ongoing

# Aggressive Conditional PKD1-KO Mouse Model of ADPKD Allows for Rapid Compound Evaluation



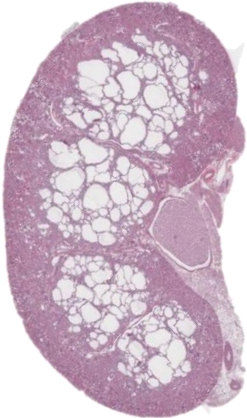
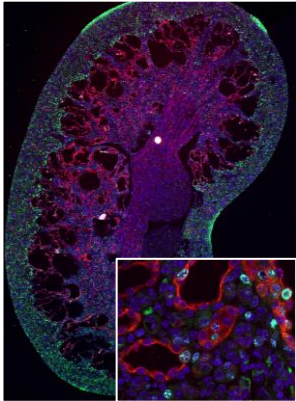
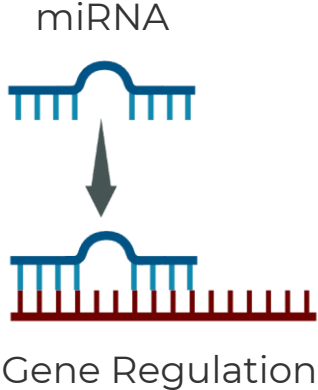
## Localization and segment identity of renal cysts in ADPKD mouse model



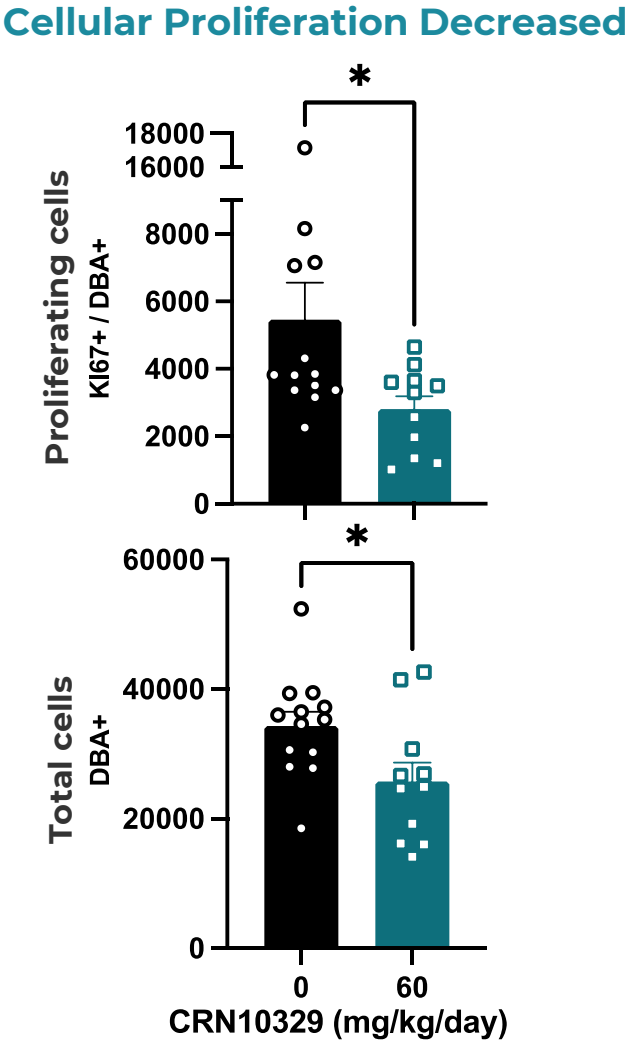
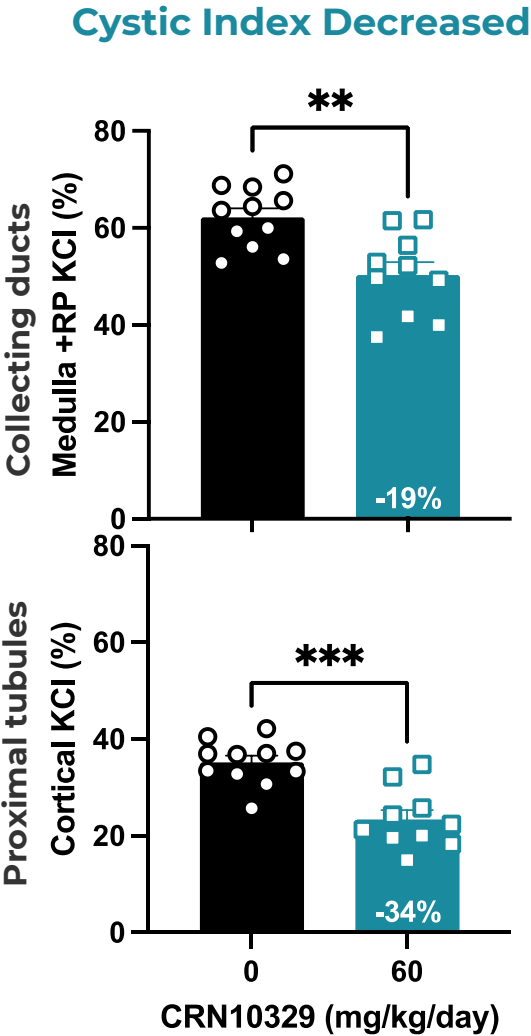
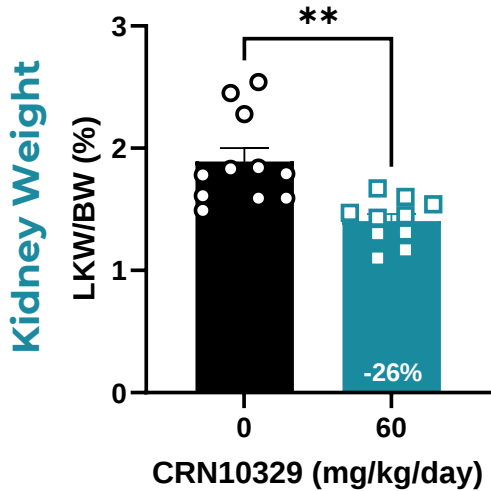
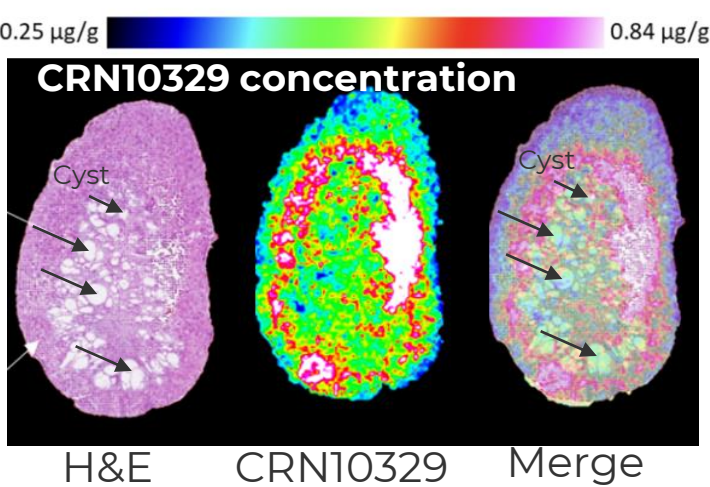
Cysts derive from collecting ducts in medulla and from proximal tubules in cortex

# A Multi-level Approach to Characterize Efficacy in ADPKD Mouse Model

Biomarkers used to interrogate efficacy of advanced SST3 agonists

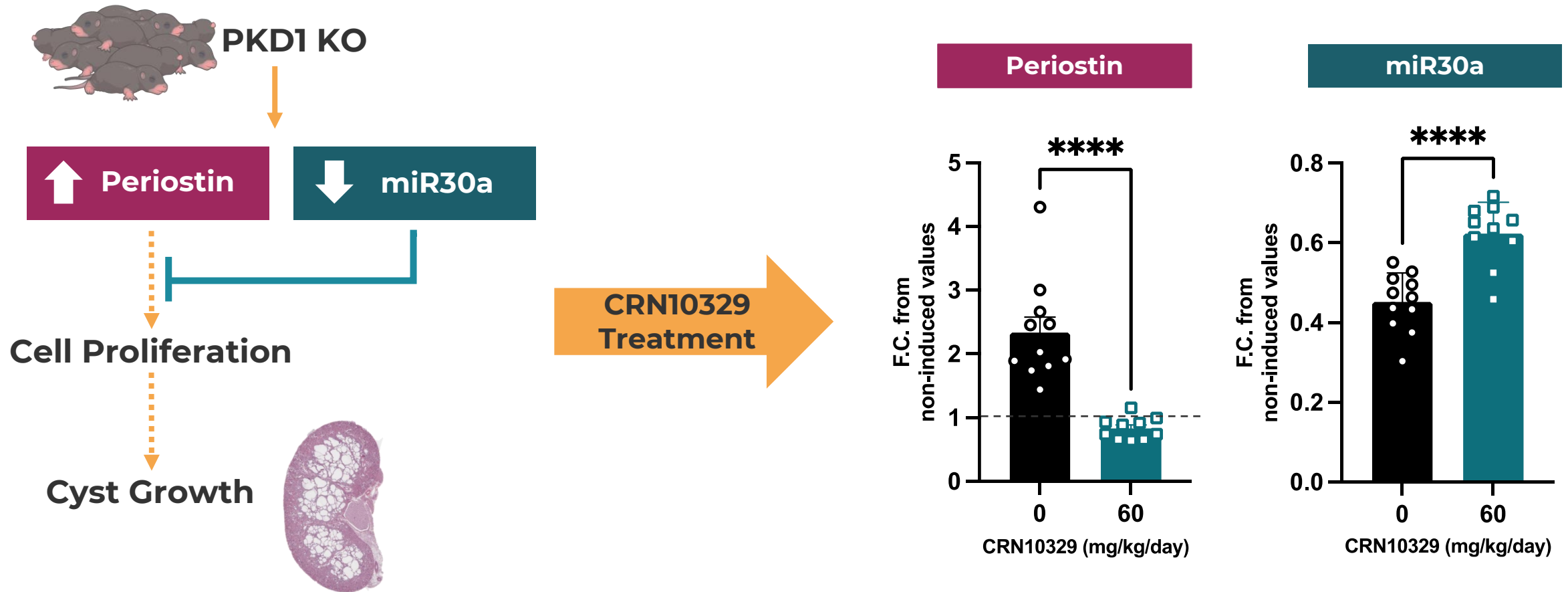
| Level     | Organ                                                                             | Tissue                                                                              | Cellular                                                                            | Molecular                                                                            |
|-----------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|           |  |  |  |  |
| Biomarker | Kidney Weight                                                                     | Cyst size                                                                           | Proliferation markers                                                               | RNA pathway profile                                                                  |

# Exposure to CRN10329 Inhibits Cyst Growth and Decreases Proliferation in an Aggressive Mouse Model of ADPKD



LKW: left kidney weight; BW: body weight.

# CRN10329 Corrects Aberrant Expression of Renal Tubular Injury Markers



# CRN10329 has the Potential to be Standard of Care for ADPKD

| TPP Comparison      | Tolvaptan<br>V2R antagonist<br><i>Current SOC</i>                                                                                                                                                                                                                                         | miRNA 17 inhibitor<br><i>Ph2/3</i>                                                                                                                                                                                                                                                                          | CRN10329<br>SST3 agonist<br><i>Preclinical</i>                                                                                                                                                                                                                                                              |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Target Indication   |  ADPKD at risk of rapid progression                                                                                                                                                                      |  ADPKD at risk of moderate to very rapid progression,                                                                                                                                                                    |  ADPKD at any risk of progression                                                                                                                                                                                        |
| Efficacy            |  ~50% reduction in total kidney volume (TKV) growth, only in first year of treatment<br> ~33% reduction in eGFR decline |  Potential for impact on TKV to be more effective than tolvaptan<br> Potential for impact on eGFR to be more effective than tolvaptan |  Potential for impact on TKV to be more effective than tolvaptan<br> Potential for impact on eGFR to be more effective than tolvaptan |
| Tolerability/Safety |  Black Box Warning: Requires continual liver monitoring<br>Hyponatremia, dehydration and hypovolemia, polyuria and nocturia significantly impact patients' lives                                        |  Mild to moderate AEs including injection site reaction, headache, and sinus infection                                                                                                                                  |  Expected to be well tolerated                                                                                                                                                                                          |
| Dosing              |  Oral BID, requires titration                                                                                                                                                                          |  SC, Q2W, no expected titration                                                                                                                                                                                        |  Oral, QD, no titration expected                                                                                                                                                                                       |

QD: Once daily  
BID: Twice daily

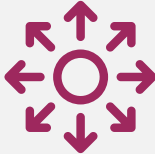
Q2W: Once every two weeks  
SC: Subcutaneous

# SST3 Agonist: First-In-Class Novel Therapy for the Majority of ADPKD Patients and Beyond

## Product Vision

To be the **first-in-class, oral, once-daily**, SST3 agonist that provides long-term **kidney function protection**, **improves** the **quality of life**, and becomes the **standard of care** for people living with ADPKD

## Strategies

|                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p><b>1. Provide a new, superior SOC:</b><br/>Establish efficacy, improve safety/tolerability, first approval in ADPKD at high risk of rapid progression (Stage 2-3A)</p> |  <p><b>2. Accelerated approval based on Phase 2 endpoint (TKV):</b><br/>Efficient clinical development plan to enable accelerated approval based on TKV endpoint</p>       |  <p><b>3. Expand to earlier, younger patients with superior safety / tolerability:</b><br/>Lifelong protection of kidney function to stop or delay renal function impairment (Stage 1)</p> |
|  <p><b>4. Expand to more advanced patients (superior efficacy):</b><br/>The first treatment to stop or delay progression to ESRD (Stages 3B-4)</p>                       |  <p><b>5. Exploit combination potential:</b><br/>Evaluate emerging preclinical and clinical data to identify potential additive or synergistic combination therapies</p> |  <p><b>6. Indication expansion:</b><br/>Explore in polycystic liver disease (PLD) and non-functioning pituitary adenomas (NFPAs)</p>                                                     |

# Next Steps for the SST3 Agonist Program



**IND Enabling Studies  
and Activities**



**IND Clearance**



**Phase 1 Healthy  
Volunteer Study**

# NONPEPTIDE DRUG CONJUGATES (NDC) PLATFORM

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**Stephen Betz, Ph.D.**

Founder & Chief Scientific Officer



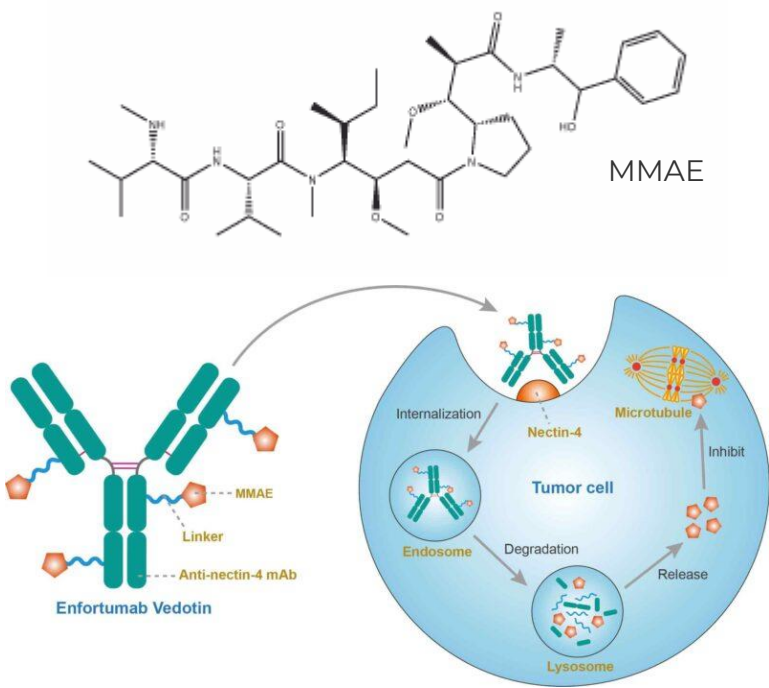
# Crinetics' Unique SST2-NDC Approach Integrates Two Validated Strategies in Oncology

SST2 is a well-established target for imaging and PRRT

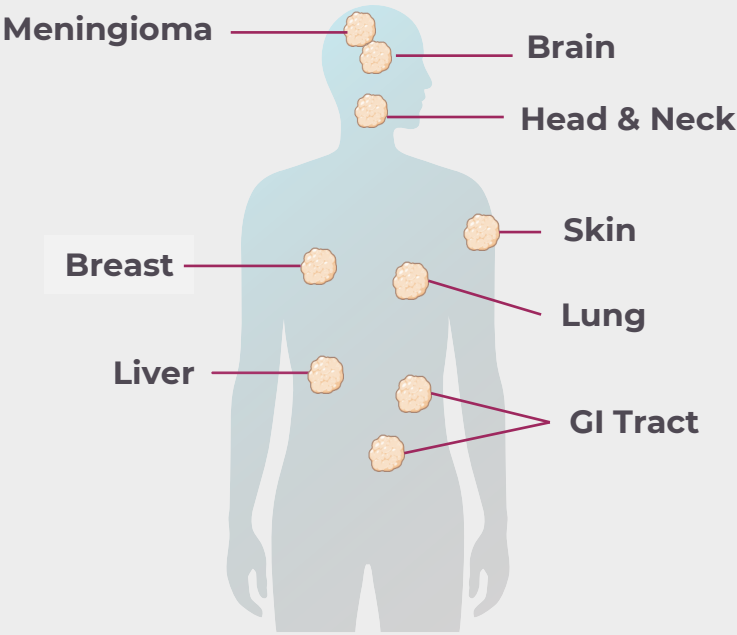


<sup>64</sup>Cu-dotatate PET scan of a patient with intestinal NET and multiple metastases

MMAE is a well-established, effective, and easily sourced anti-tumor payload

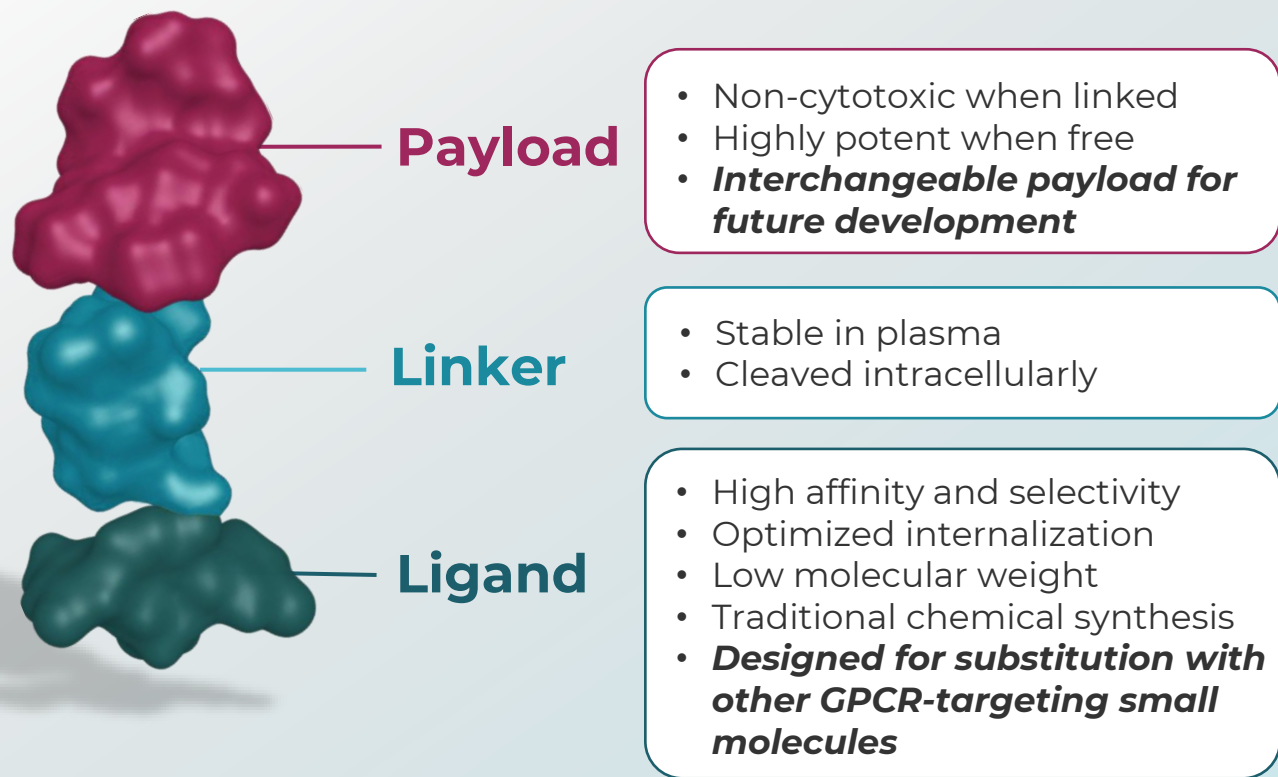


## Broad Indication Potential



Pauwels (2018) Am J Nuc Med 8, 311-331

# NDCs Are Designed to Selectively Target and Deliver Cytotoxic Payloads to Cells of Interest



Applicability across multiple endocrinology and endocrine-adjacent therapeutic areas including oncology and immunology

## Differentiation vs. Current Modalities

### ● **Anticancer Agents** (Chemotherapies)

- ✗ Not tumor specific
- ✗ Unfavorable PK/ADME
- ✗ Narrow therapeutic index

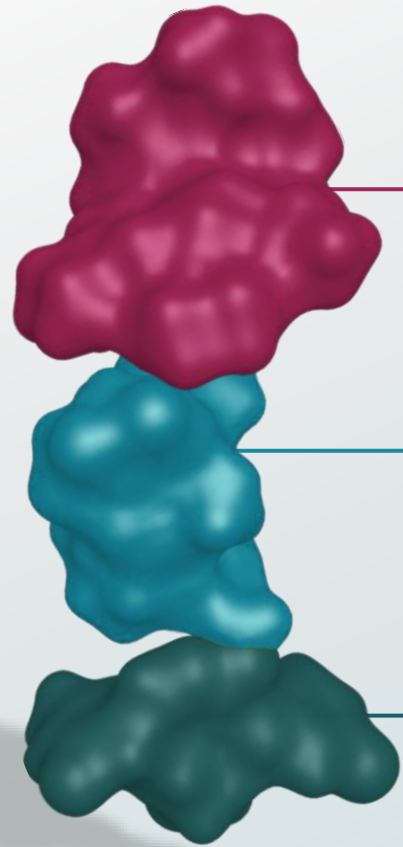
### Y● **Antibody-Drug Conjugates**

- ✗ Long half-life
- ✗ Poor tumor penetration
- ✗ Unspecific uptake

### ◀☢ **Radioligand Therapies**

- ✗ Limited number of cycles
- ✗ Radionuclide supply
- ✗ Treatment logistics
- ✗ Radiation safety

# CRN09682 is the First of Many Potential NDCs from this Platform



**MMAE**

- Known to kill cells of interest
- Not toxic when conjugated
- Long in-tumor stability

**Linker**

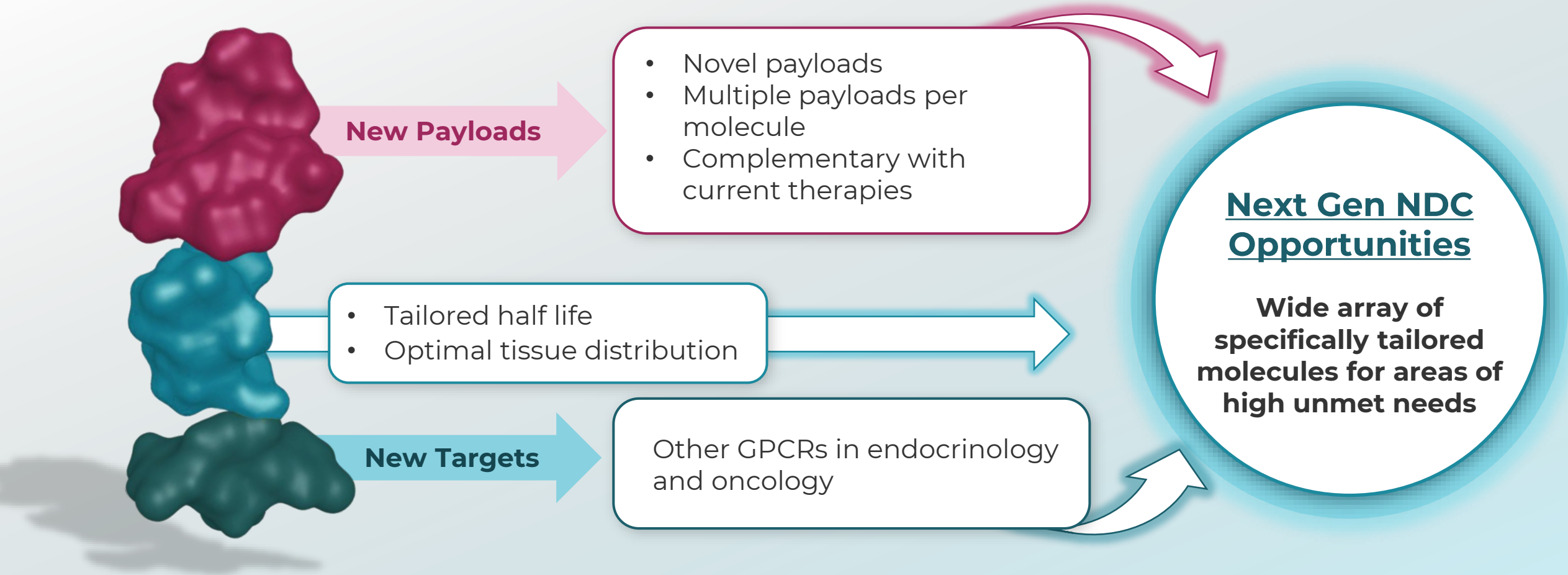
- Stable in plasma
- Rapidly and specifically cleaved when internalized
- Does not interfere with pharmacology

**SST2  
Agonist**

- Potent SST2 agonist
- Selective for SST2
- Optimized for internalization
- Stable in plasma

## Each Component is Optimized

# Next Steps for the Crinetics NDC Platform: Leverage Tailoring of Components for Specific Patient Needs



# NENS

## NEUROENDOCRINE NEOPLASMS

---

**DAVID C. METZ, MBBCH**

Professor of Medicine (retired)

Neuroendocrinologist



# Neuroendocrine Neoplasms (NENs): Rare Tumors Arising from Neuroendocrine Cells Throughout the Body

- NENs originate in wide range of organs
- **SST2 expressed on ~80%** of tumors<sup>1</sup>
- Spectrum of disease from **well-differentiated**, indolent neuroendocrine tumors (**NETs**) to **poorly-differentiated**, highly aggressive neuroendocrine carcinomas (**NECs**), including small-cell lung cancer (SCLC)
- Often present at advanced, incurable stage with **>50% metastatic** typically to liver<sup>2</sup>
- Clinically, **nonfunctional or functional** based on symptoms of hormone hypersecretion (e.g. **carcinoid syndrome**)

## Gastrointestinal (GI) NETs

(also referred to as carcinoid tumors)

### Foregut

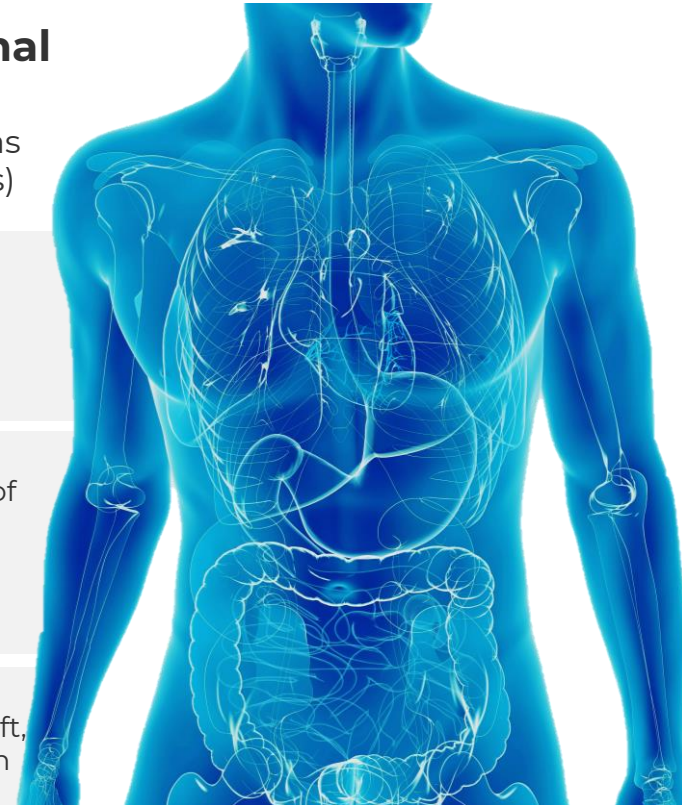
- Lungs
- Stomach
- First part of duodenum

### Midgut

- Second part of duodenum
- Jejunum
- Ileum
- Right Colon

### Hindgut

- Transverse, left, sigmoid colon
- Rectum



## Pancreatic NETs

(functional/non-functional)

## Most common primary sites:

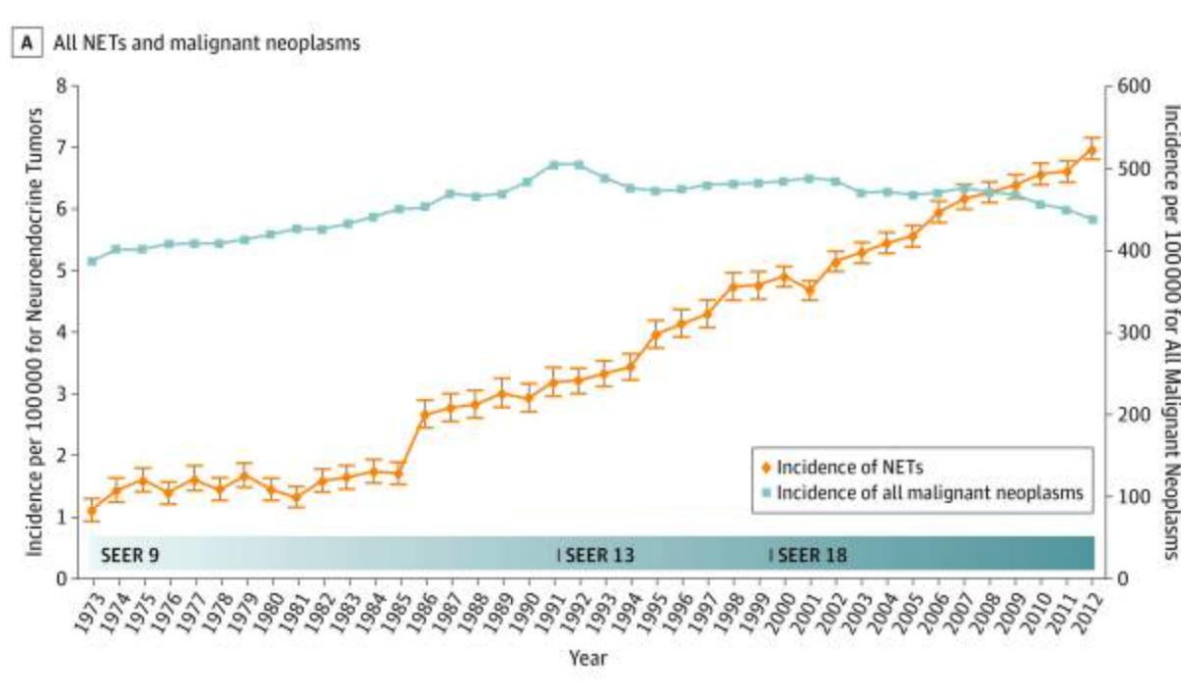
Extra-pulmonary

- Pancreas
- GI tract
- Lungs

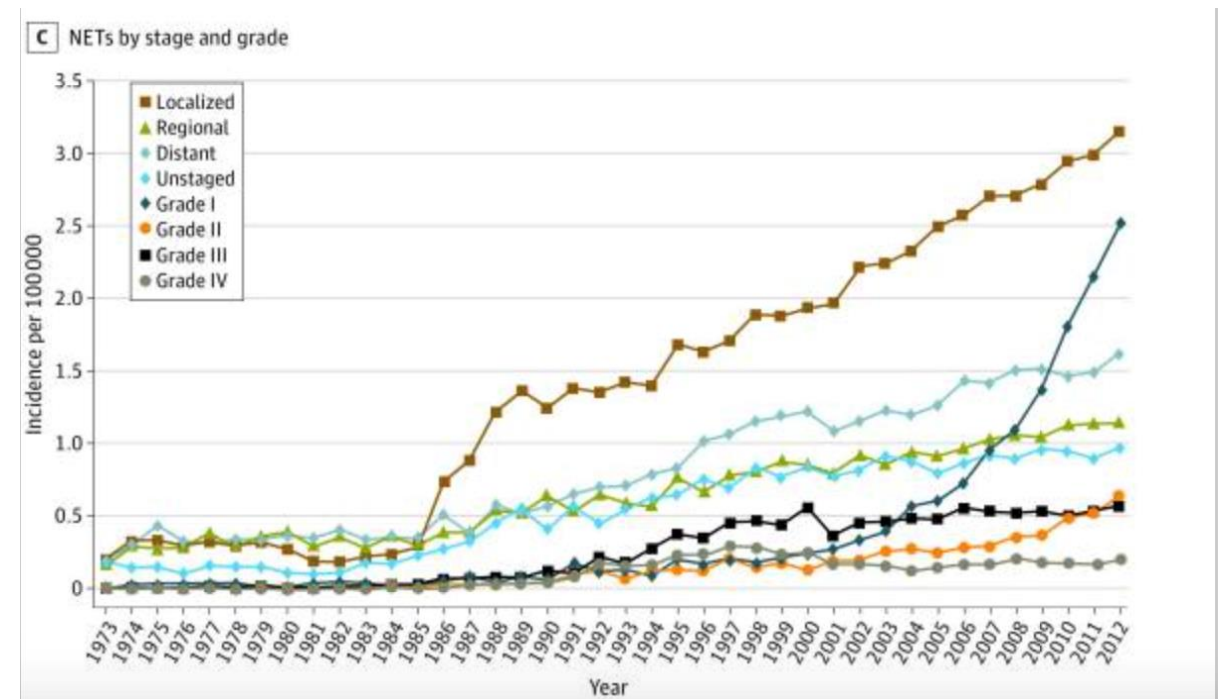
Extra-pancreatic

# Incidence of Neuroendocrine Tumors is Increasing Over Time

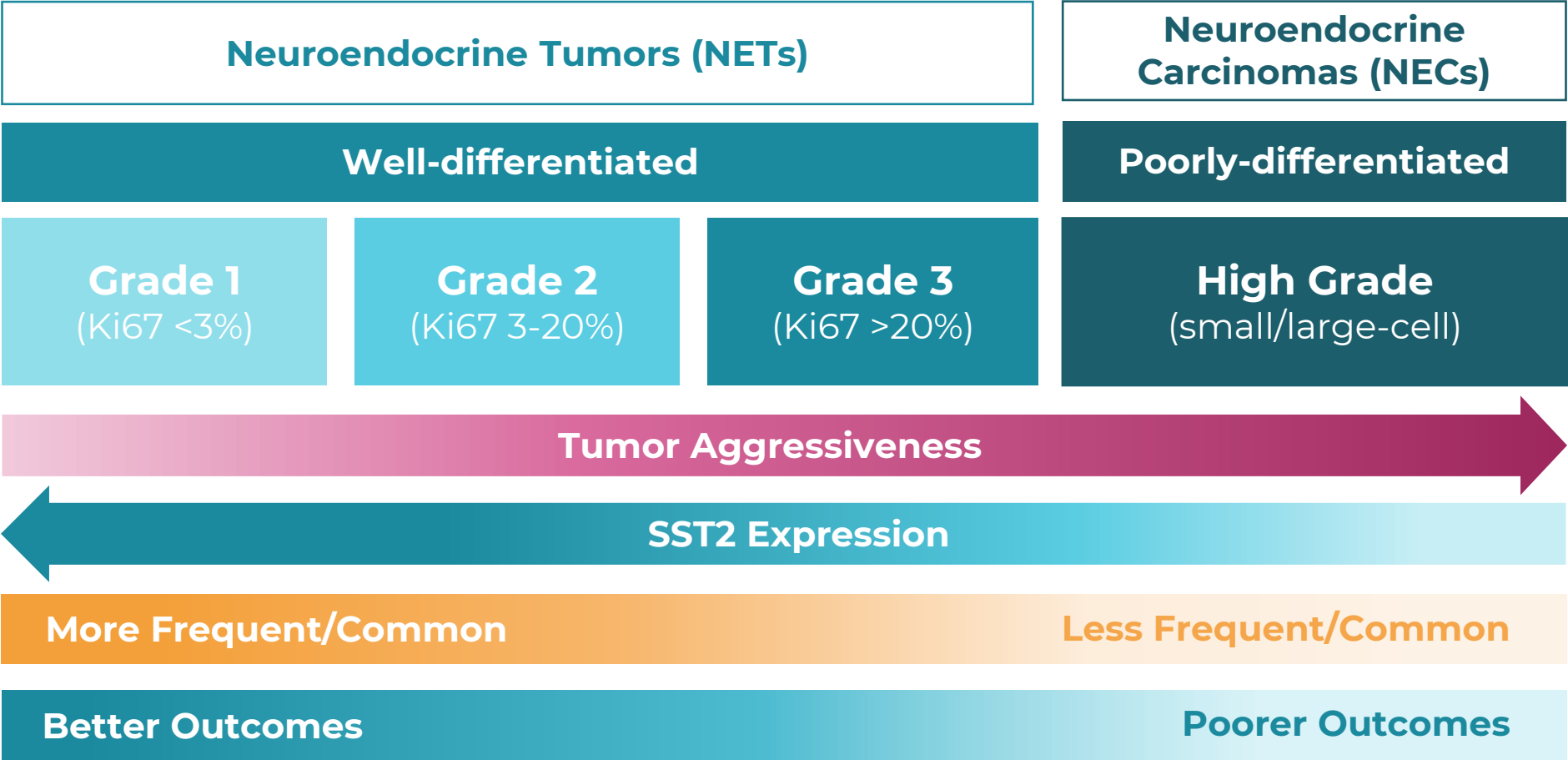
## NETs Incidence has Increased Faster than Other Malignancies



## The Increase Affects All Grades and Stages



# NENs are Rare, Heterogenous and Treated Based on the Tumor Grade & Differentiation

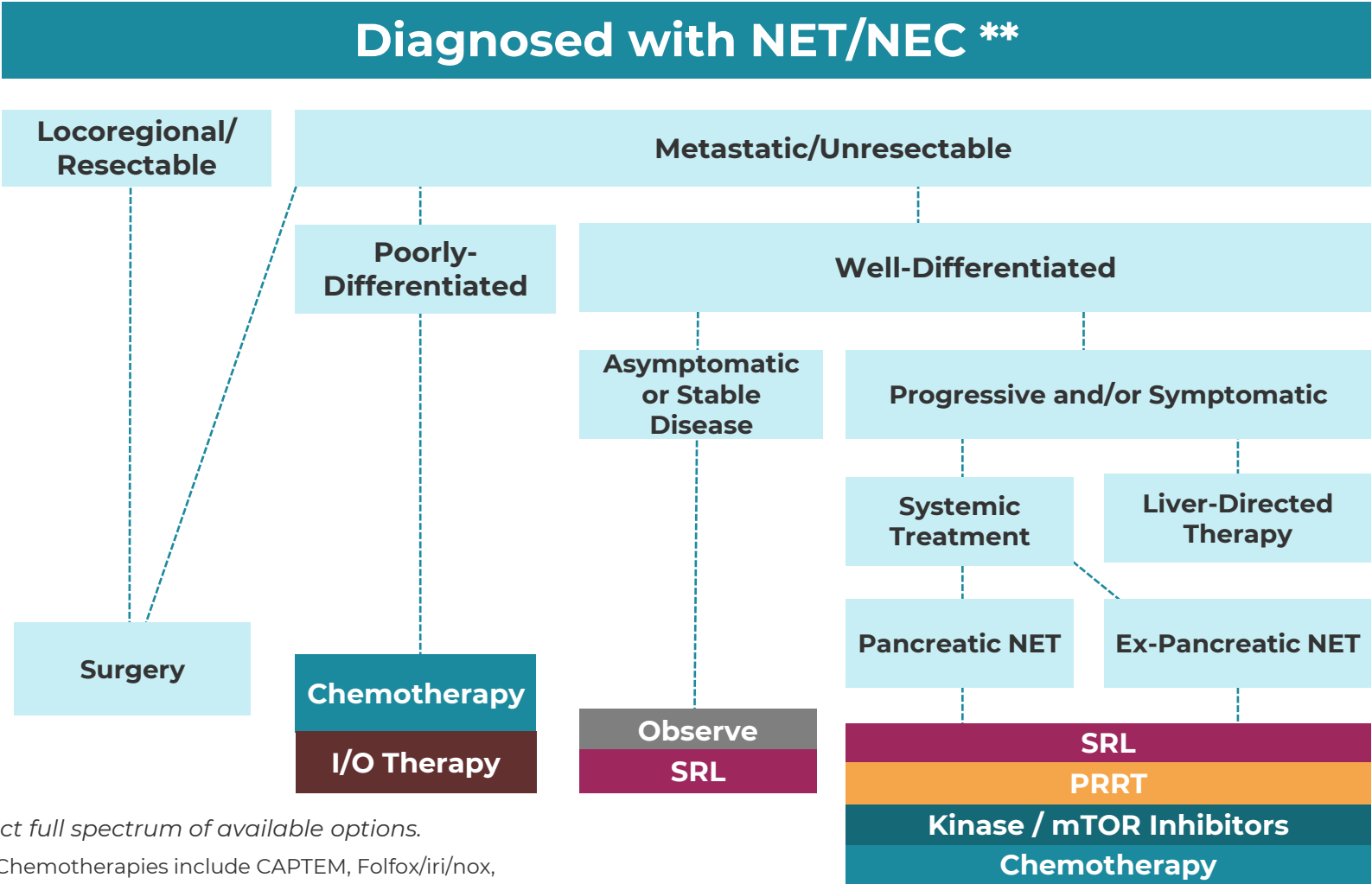


# NEN Treatment Algorithm is Complex

There is no consensus on order of treatments for advanced metastatic disease

## Major Outcome Predictors\*:

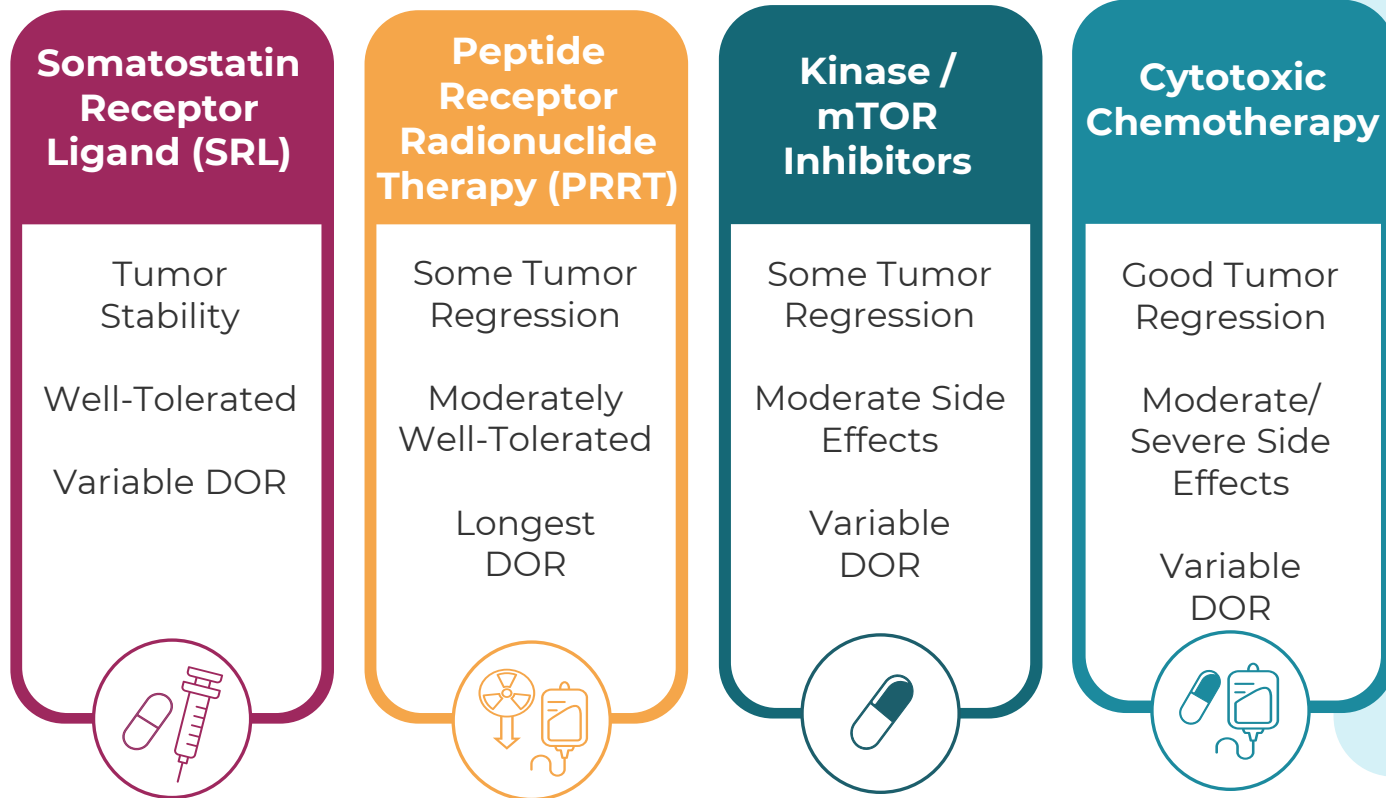
- Stage (extent of disease)
- Grade and differentiation
- Primary tumor site
- Patient age (<50 yo vs. ≥50 yo)



Treatments represent most commonly used but do not reflect full spectrum of available options.  
Kinase / mTOR inhibitors include Cabozantinib, Everolimus, Sunitinib. Chemotherapies include CAPTEM, Folfox/iri/nox, platinum/etoposide, Lurbinectedin, I/O: Immunotherapies

# Neuroendocrine Neoplasms (NENs) are Incurable When Metastatic, Regardless of Grade

## Expected Treatment Outcomes



## A significant opportunity exists for a new therapy that....

- ✓ Kills tumor cells rapidly and effectively
- ✓ Improves efficacy for higher grade disease
- ✓ Addresses PRRT intolerance and cycle limitations
- ✓ Provides better benefit/risk profile after SRL use
- ✓ Improves quality of life and survival

# CRN09682

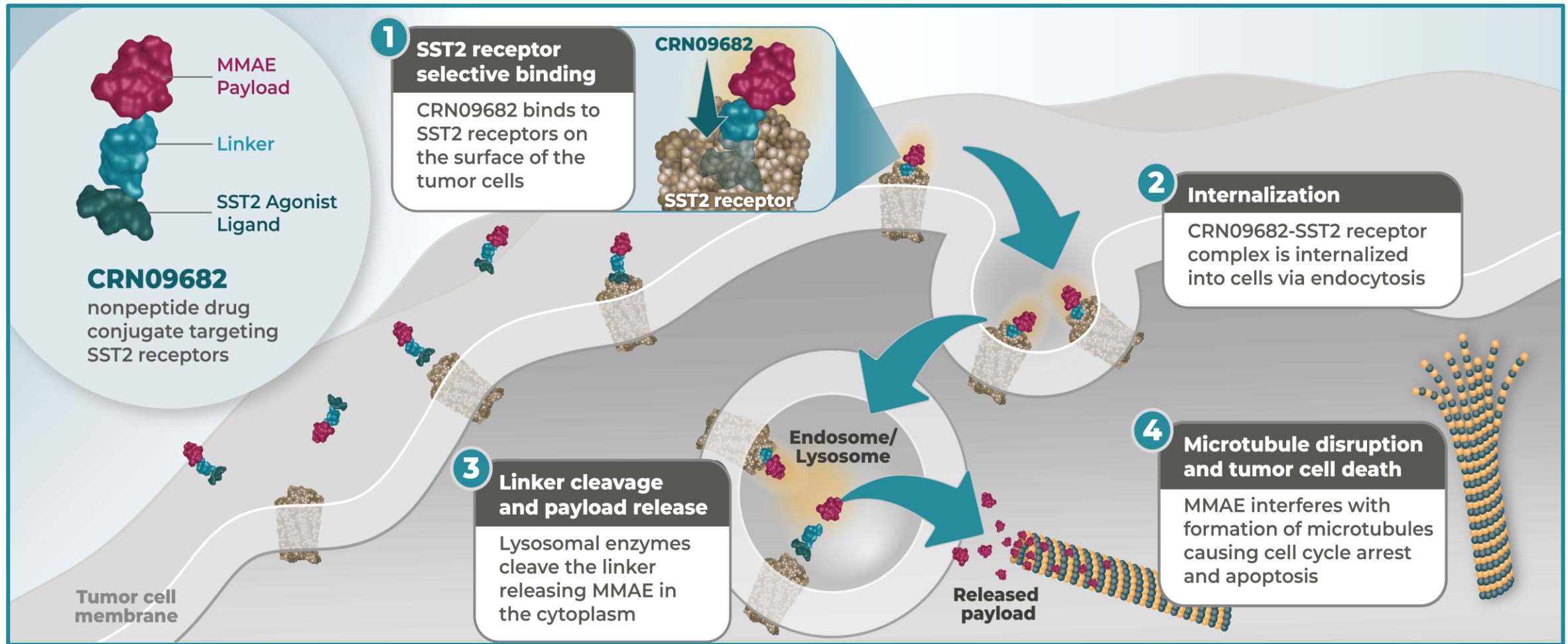
SST2+ CANCERS:  
Neuroendocrine Tumors and Beyond

**Stacey Harte**

Global Product Leader, CRN09682



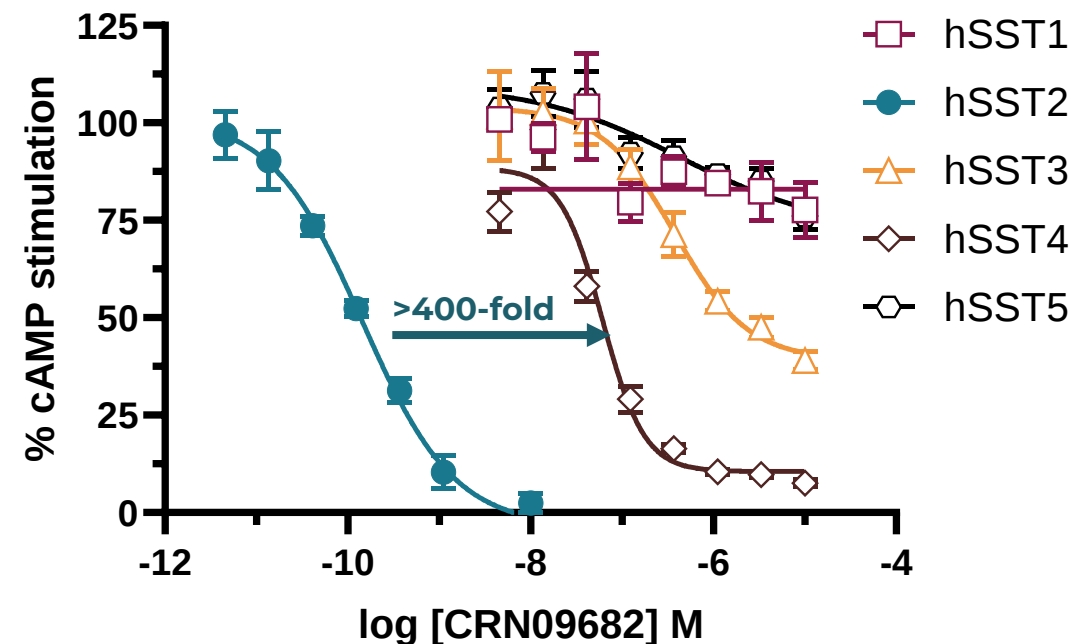
# CRN09682 is a First-in-Class Therapy Designed to Selectively Target and Deliver MMAE to SST2-Expressing Tumor Cells



# CRN09682 was Purposefully Designed to be Selective for and Internalized by SST2

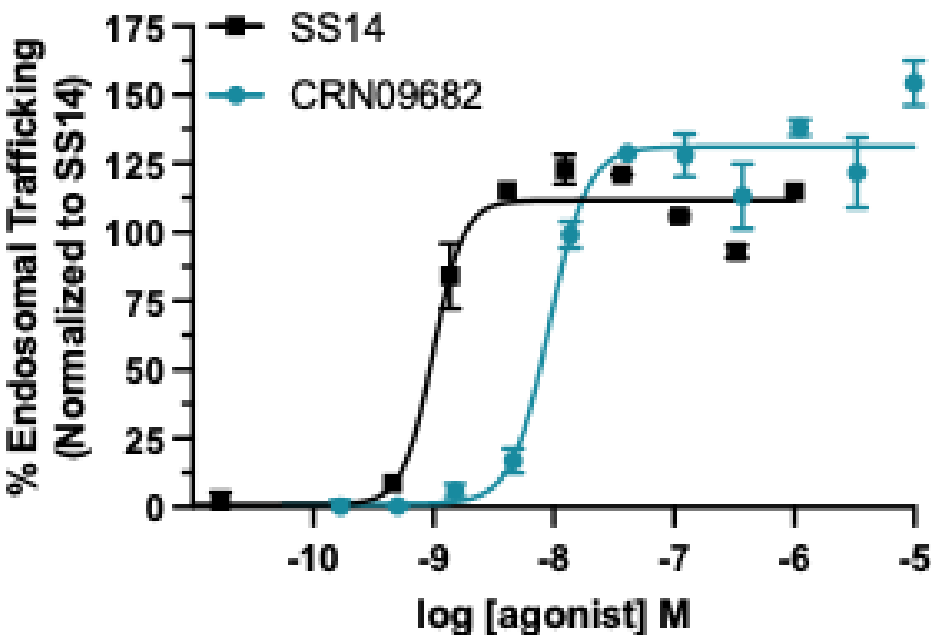
## Potency and Selectivity

cAMP production assay



## SST2 Internalization

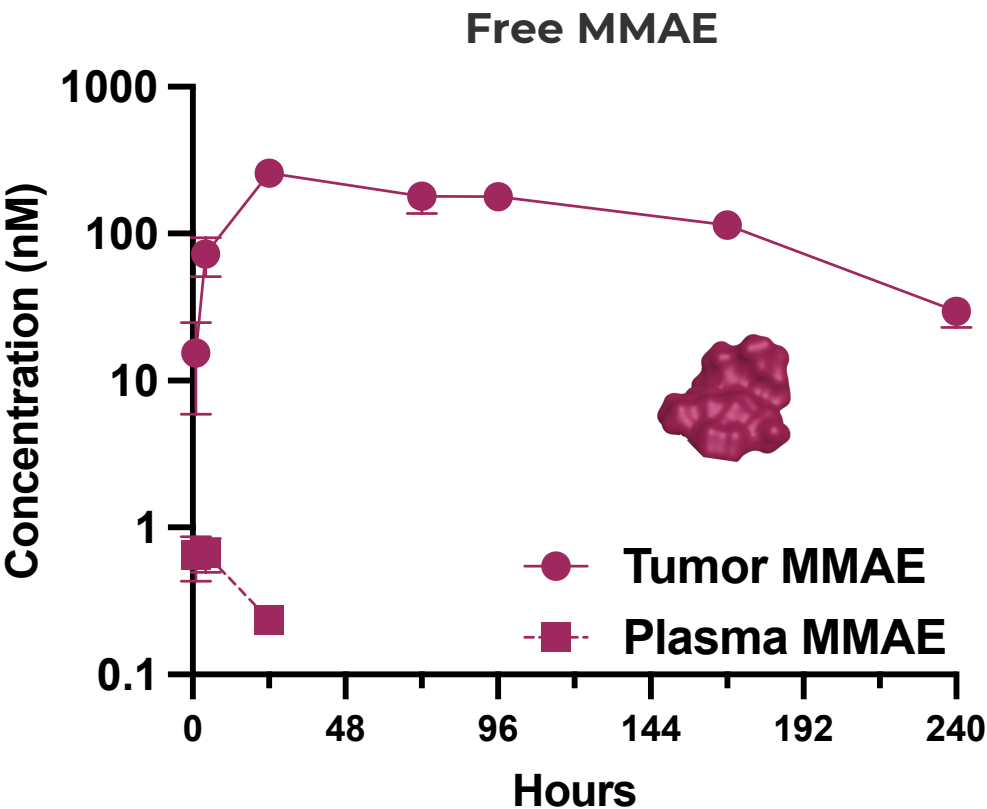
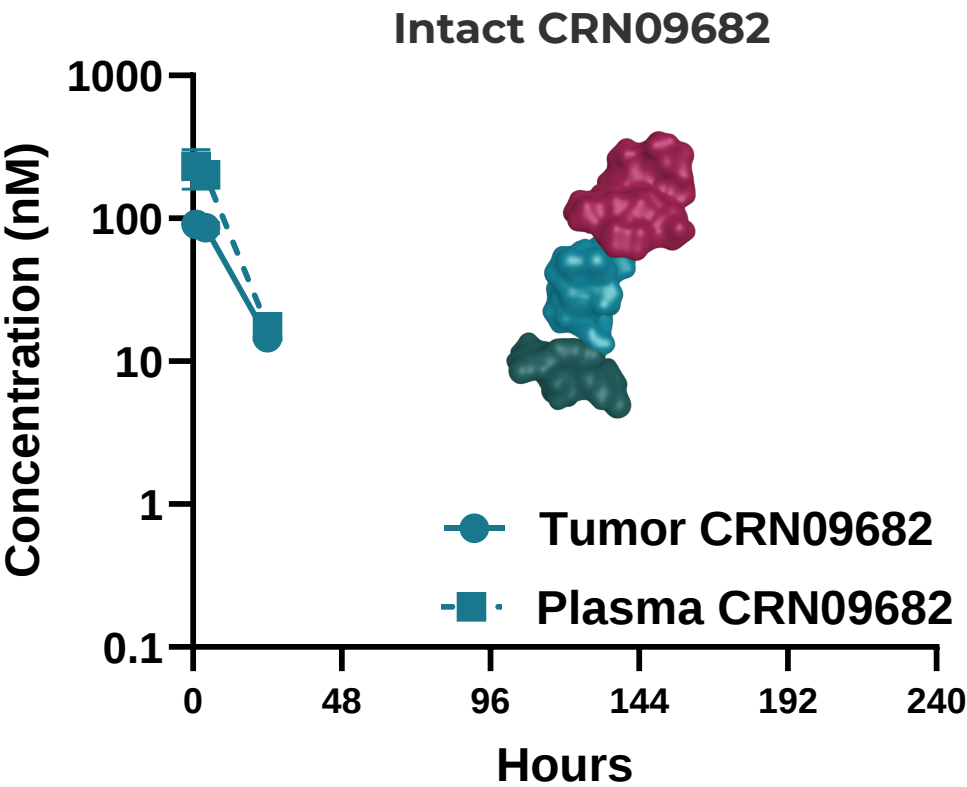
Endosomal trafficking assay



SS14 is native somatostatin, peptide hormone agonist of SST2

# CRN09682 Selectively Delivered MMAE into SST2+ Tumors with Minimal Systemic Exposure to Free MMAE

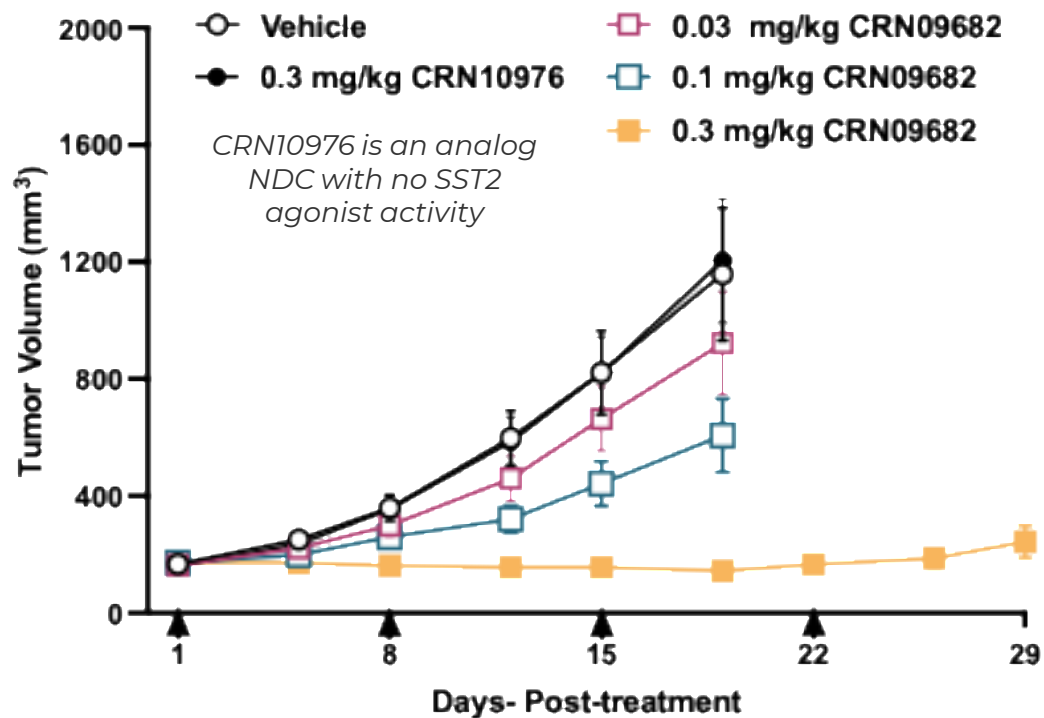
## Tumor PK in Nude Mice Bearing SCLC SST2-Expressing NCI-H524 Tumors



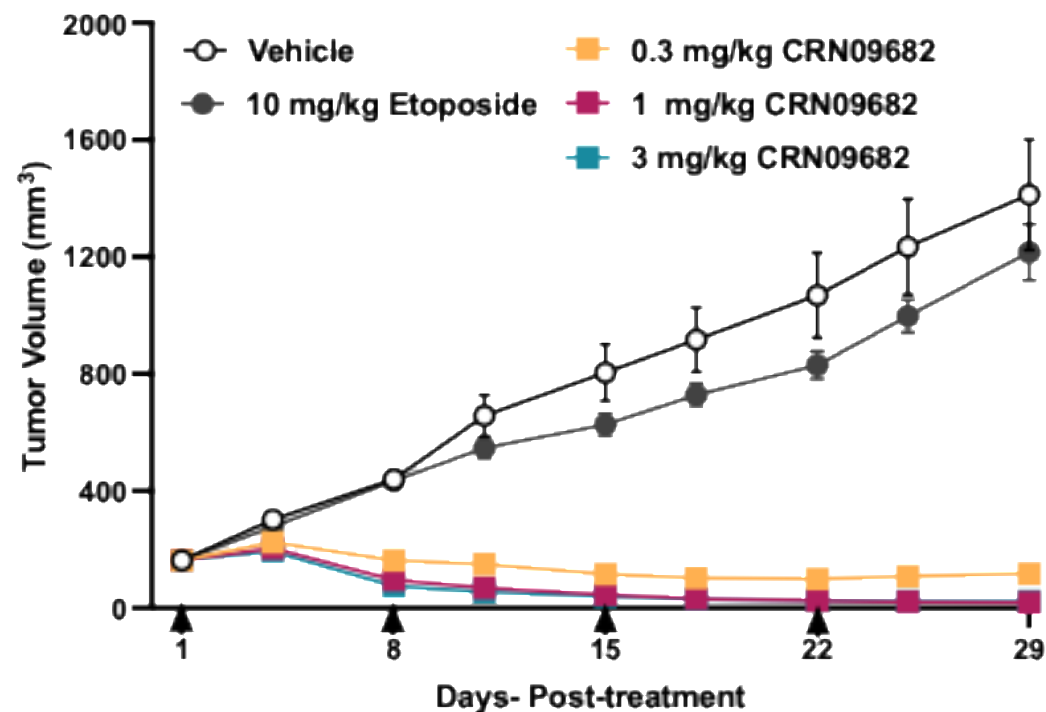
Single IV dose of CRN09682 0.3 mg/kg administered to CDX mice

# CRN09682 Inhibited Tumor Growth in Two SCLC SST2 Expressing CDX Mouse Models in a Dose-Dependent Manner

## CRN09682 Efficacy Study in NCI-H524 Tumor Model



## CRN09682 Efficacy Study in NCI-H69 Tumor Model

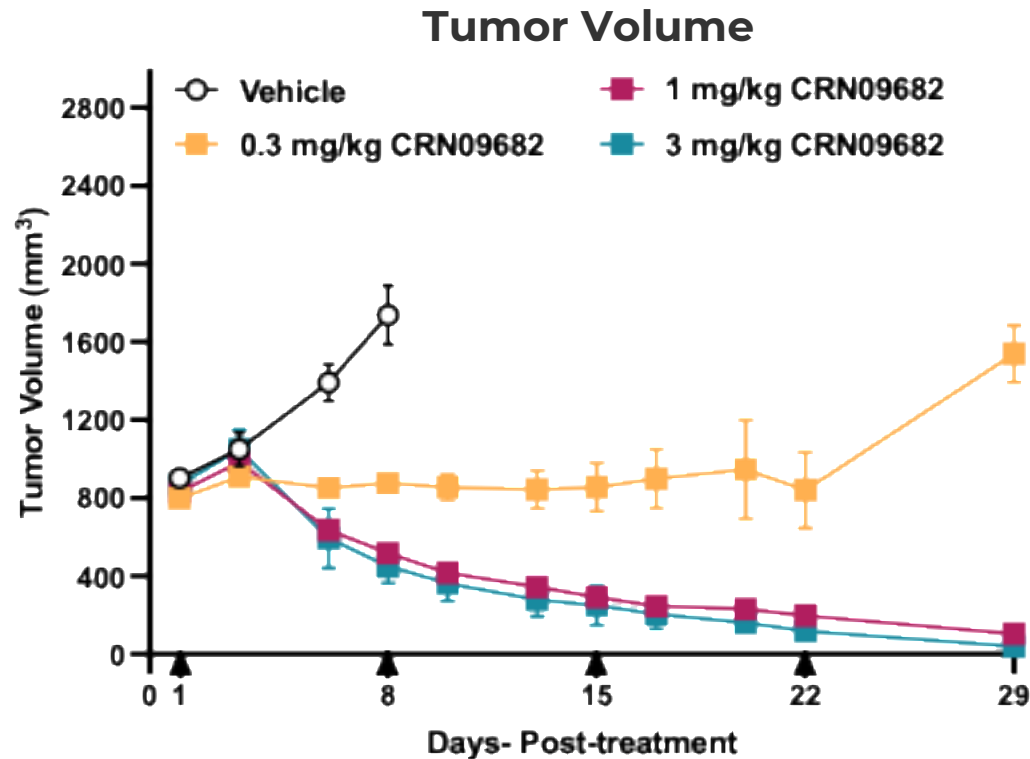


Dosing QWx4 wks in both studies.

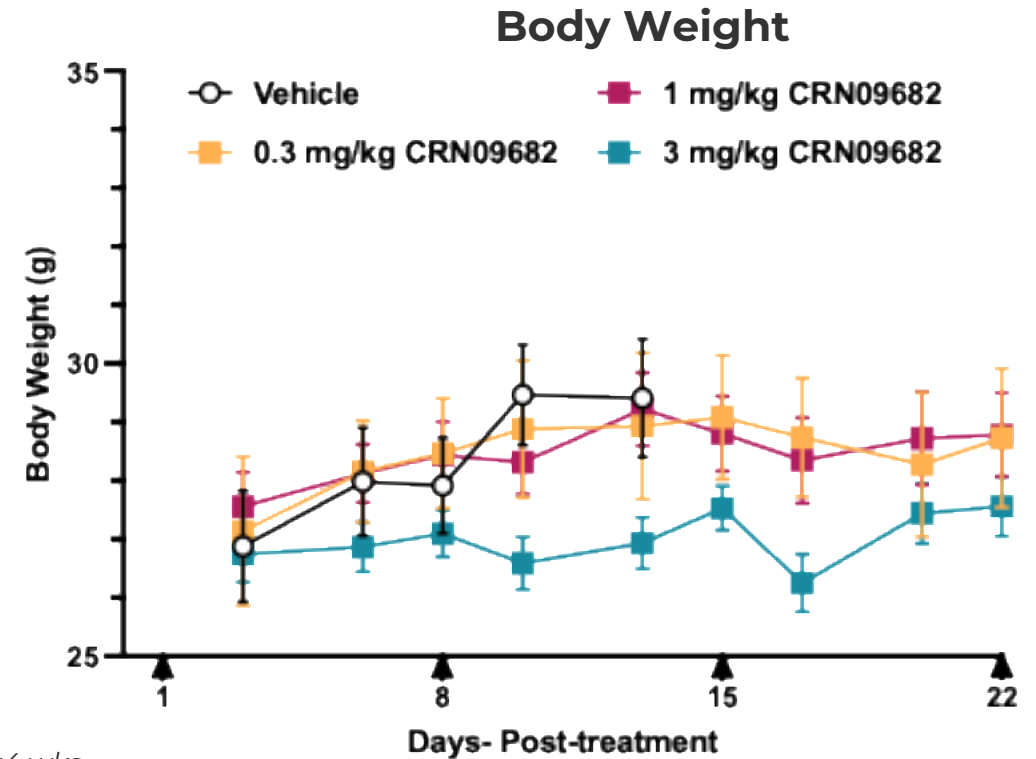
- CRN09682 demonstrated anti-tumor activity in both models and induced tumor regression in NCI-H69 model
- CRN09682 had no effect on BW in NCI-H524 and induced minimal BW loss at 3 mg/kg in NCI-H69 model

# CRN09682 Induced Rapid Tumor Regression in SCLC CDX Mice Bearing Large Tumors

## CRN09682 Efficacy Study & Body Weights in NCI-H524 Tumor Model



*Dosing QWx4 wks.*



- CRN09682 demonstrated anti-tumor activity and induced tumor regression at 1 and 3 mg/kg
- Complete regression observed in 3/10 mice at 1 mg/kg and 7/10 mice at 3 mg/kg
- CRN09682 had no effect on BW loss in NCI-H524 model

# CRN09682 Phase 1/2 Study

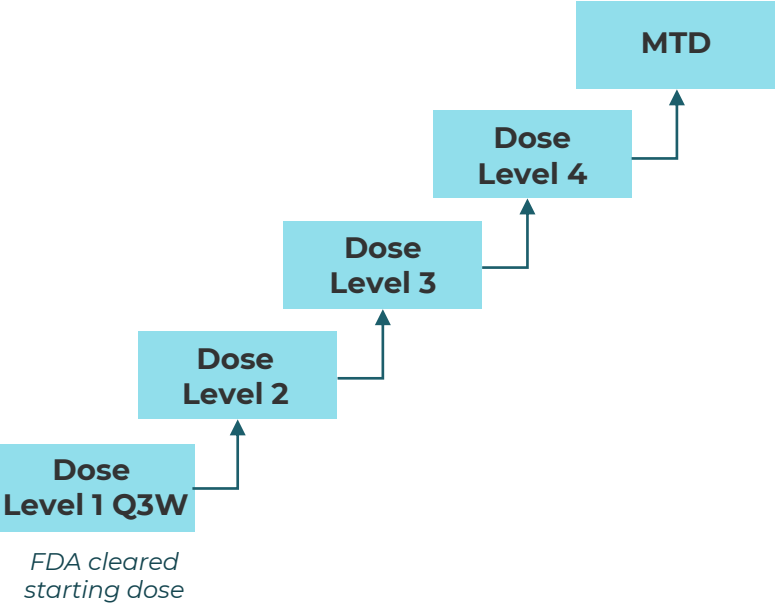


## Key Eligibility Criteria:

- Metastatic or locally advanced inoperable NETs, NECs or other solid tumors
- Tumor progression on or after last line of therapy
- Positive SSTR expression by FDA approved SSTR PET/CT
- No carcinoid syndrome

## Ph 1: Dose Escalation

- Bayesian Optimal Interval design, n=3-6/cohort



## Ph 2: Dose Expansion\*

- n=approximately 25/cohort

Recommended Expansion Dose

- Cohort 1: Pancreatic NET Well-differentiated**
- Cohort 2: ex-Pancreatic NET Well-differentiated**
- Cohort 3: NEC Poorly Differentiated (includes SCLC)**
- Cohort 4: Other Solid Tumors (e.g. Breast, Head-Neck)**

\*representative of potential cohorts



## Key Endpoints

- Safety & tolerability of CRN09682
- Define DLT/MTD and select Expansion Dose
- PK of CRN09682 and MMAE

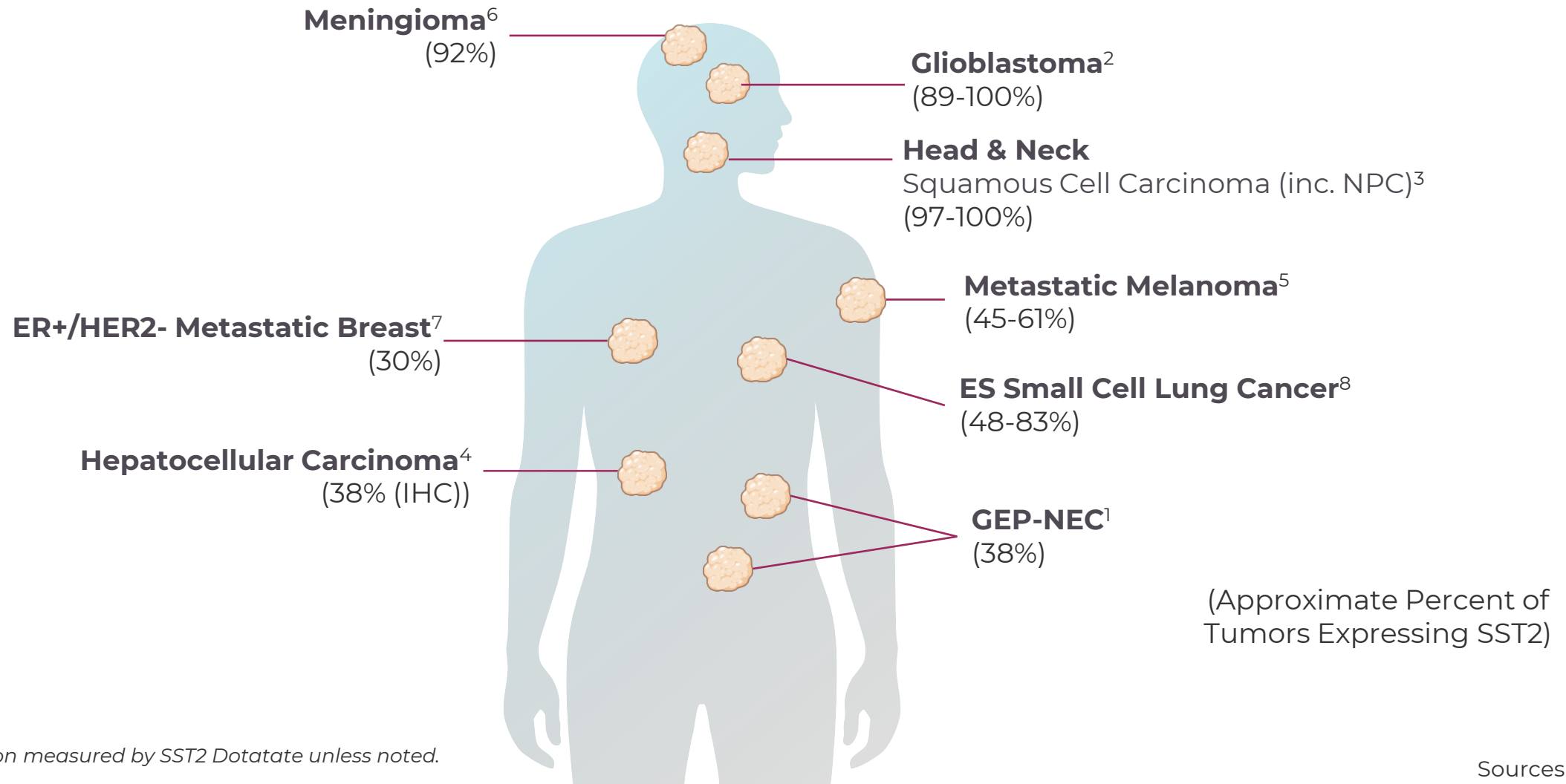


## Efficacy Endpoints

- Measure preliminary anti-tumor activity of CRN09682: ORR, DOR, PFS by RECIST v1.1

DLT: Dose limiting toxicity; DOR: duration of response; MTD: Maximum tolerated dose; MMAE: monomethyl auristatin E; NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor; ORR: objective response rate; PFS: progression free survival; PK: pharmacokinetics; Q3W: every 3 weeks; SCLC: small cell lung cancer); SSTR: somatostatin receptor; WD: well-differentiated

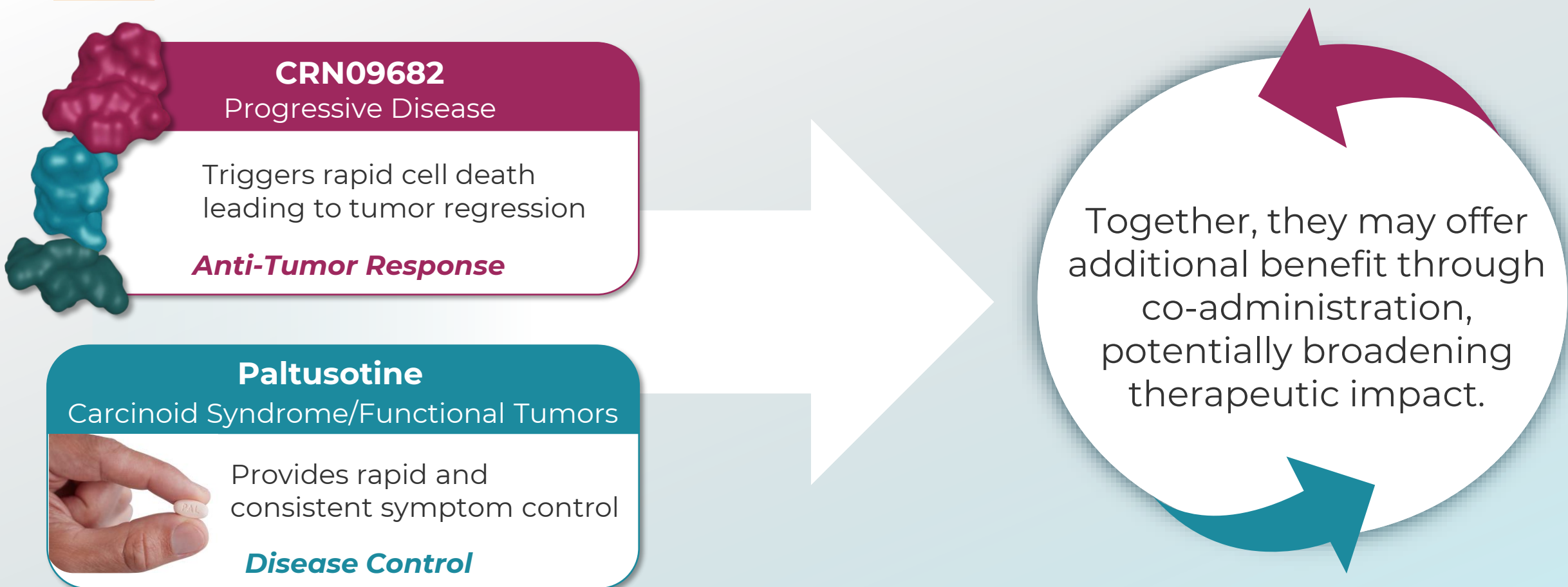
# Expanding CRN09682 Opportunity into a Broad Set of Indications by Targeting SST2+ Tumors



\* SST2 expression measured by SST2 Dotatate unless noted.

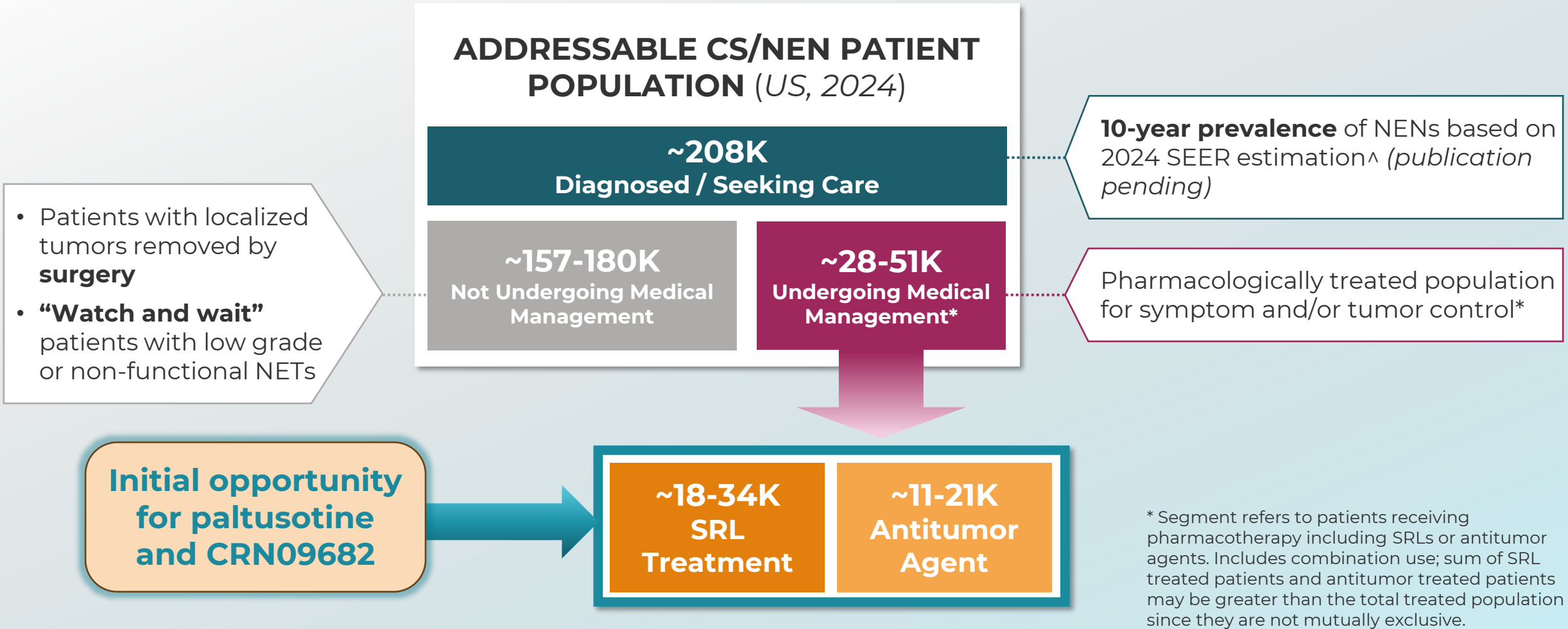
Sources in notes.

# Paltusotine and CRN09682 Have the Potential to be Distinct, Complementary Treatment Options for NETs Patients



***Crinetics' Strategy Unlocks the Full Potential to Treat the Broadest Set of NETs Patients***

# Availability of Additional Treatment Options May Expand the Limited Pharmacotherapy Use in NENs



<sup>^</sup>Source: SEER 17 & SEER 8 (Surveillance, Epidemiology, and End Results) Health Advances analysis, data on file.

NEN/Ts: neuroendocrine neoplasms/tumors; SRL: somatostatin receptor ligand

# Next Steps for the CRN09682 Program and NDC Platform



**Enrolling Patients  
in Phase 1/2 Study**



**Data from  
Dose Escalation  
Portion of Phase  
1/2 Study**



**Exploring  
Additional Tumor  
Types with  
CRN09682  
Beyond NETs**



**Expansion of  
Crinetics NDC  
Discovery Pipeline**

**BRAVESST<sub>2</sub>**  
**STUDY**

# CLOSING REMARKS

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**Scott Struthers, Ph.D.**

Founder & Chief Executive Officer



# Continued Value Creation with Deep Pipeline of Transformative Drug Candidates

| Program                                       | Discovery                                  | IND-Enabling | Phase 1 | Phase 2 | Phase 3 | Registrational | Upcoming Milestones              |
|-----------------------------------------------|--------------------------------------------|--------------|---------|---------|---------|----------------|----------------------------------|
| <b>Paltusotine<br/>(SST2 agonist)</b>         | Acromegaly (US)                            |              |         |         |         |                | PDUFA Date (September 2025)      |
|                                               | Acromegaly (EU)                            |              |         |         |         |                | CHMP Opinion (1H 2026)           |
|                                               | Carcinoid syndrome                         |              |         |         |         |                | Phase 3 (2H 2025)                |
| <b>Atumelnant<br/>(ACTH antagonist)</b>       | Congenital adrenal hyperplasia (adult)     |              |         |         |         |                | Phase 3 in Adult (2H 2025)       |
|                                               | Congenital adrenal hyperplasia (pediatric) |              |         |         |         |                | Phase 2/3 in Pediatric (2H 2025) |
|                                               | ACTH-dependent Cushing's syndrome          |              |         |         |         |                | Phase 2/3 (2H 2025)              |
| <b>CRN09682<br/>Nonpeptide drug conjugate</b> | NETs and SST2-expressing solid tumors      |              |         |         |         |                | Phase 1/2                        |
| <b>TSH antagonist</b>                         | Graves' disease & TED                      |              |         |         |         |                | IND                              |
| <b>SST3 agonist</b>                           | ADPKD                                      |              |         |         |         |                | IND                              |
| <b>PTH antagonist</b>                         | Hyperparathyroidism                        |              |         |         |         |                | IND                              |
| <b>Oral GLP-1 nonpeptide</b>                  | Obesity                                    |              |         |         |         |                | Candidate Selection              |
| <b>Oral GIP nonpeptide</b>                    | Obesity                                    |              |         |         |         |                | Candidate Selection              |

## Partners:



**SANWA KAGAKU KENKYUSHO CO., LTD.**  
Japan Development and Commercialization  
Partner for Paltusotine



Licensee of targeted, nonpeptide  
radiopharmaceuticals



Licensee of CRN01941 for  
veterinary use

SST: somatostatin receptor type; ACTH: adrenocorticotrophic hormone; NETs: Neuroendocrine tumors; TSH: thyroid-stimulating hormone; TED: thyroid eye disease; ADPKD: Autosomal dominant polycystic kidney disease; PTH: parathyroid hormone; GLP-1: glucagon-like peptide-1 receptor agonists; GIP: gastric inhibitory polypeptide; IND: Investigational New Drug Application; PDUFA: Prescription Drug User Fee Act; CHMP: Committee for Medicinal Products for Human Use

# Crinetics of Tomorrow: A Premier, Endocrine-Focused Global Biopharmaceutical Company

**2025**

Commercial Build  
Potential US Launch

**2026 & Beyond**

Multiple Pipeline Readouts  
Potential International  
Launches

**World Class R&D  
Strong Balance Sheet**

**Sales Funded Growth  
Pipeline Expansion**



Thank You

